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ARCHIVES OF DISEASE IN CHILDHOOD

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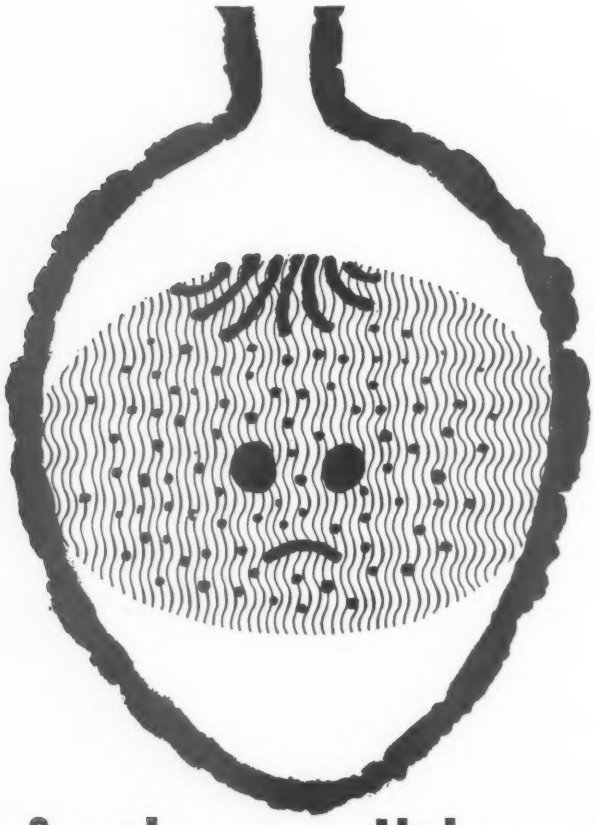

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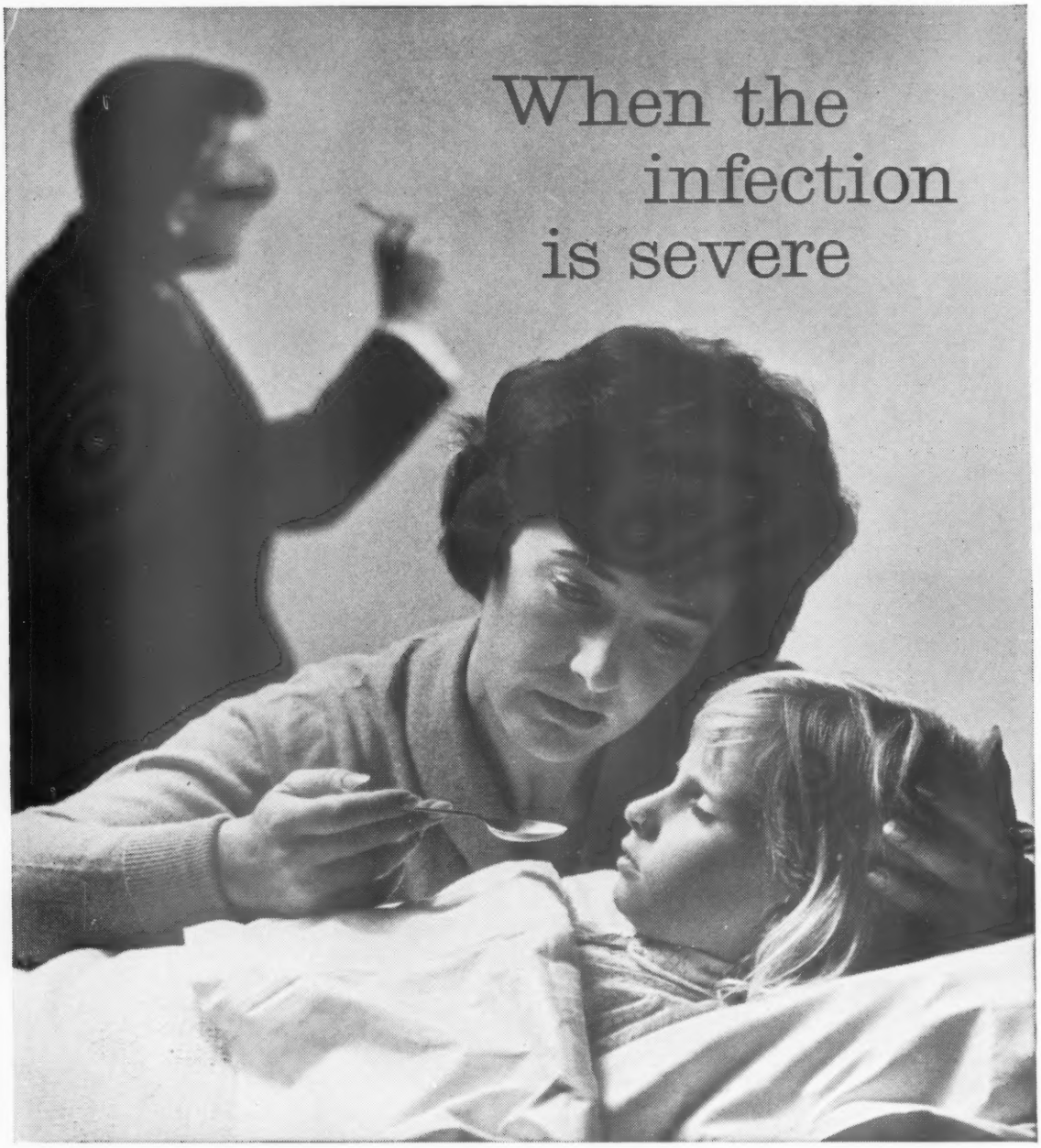

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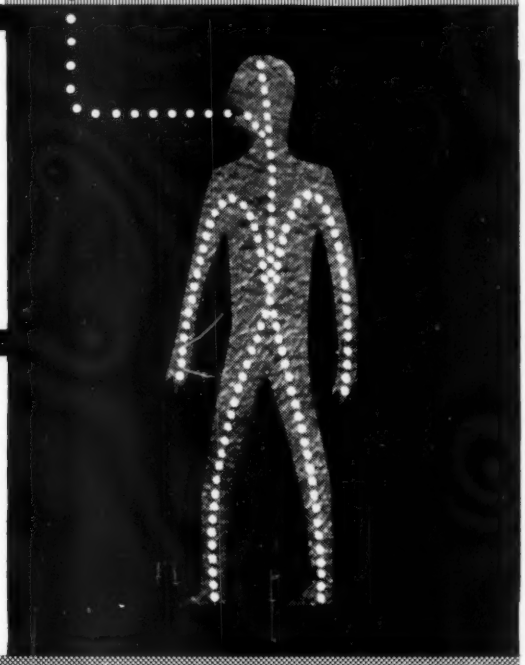

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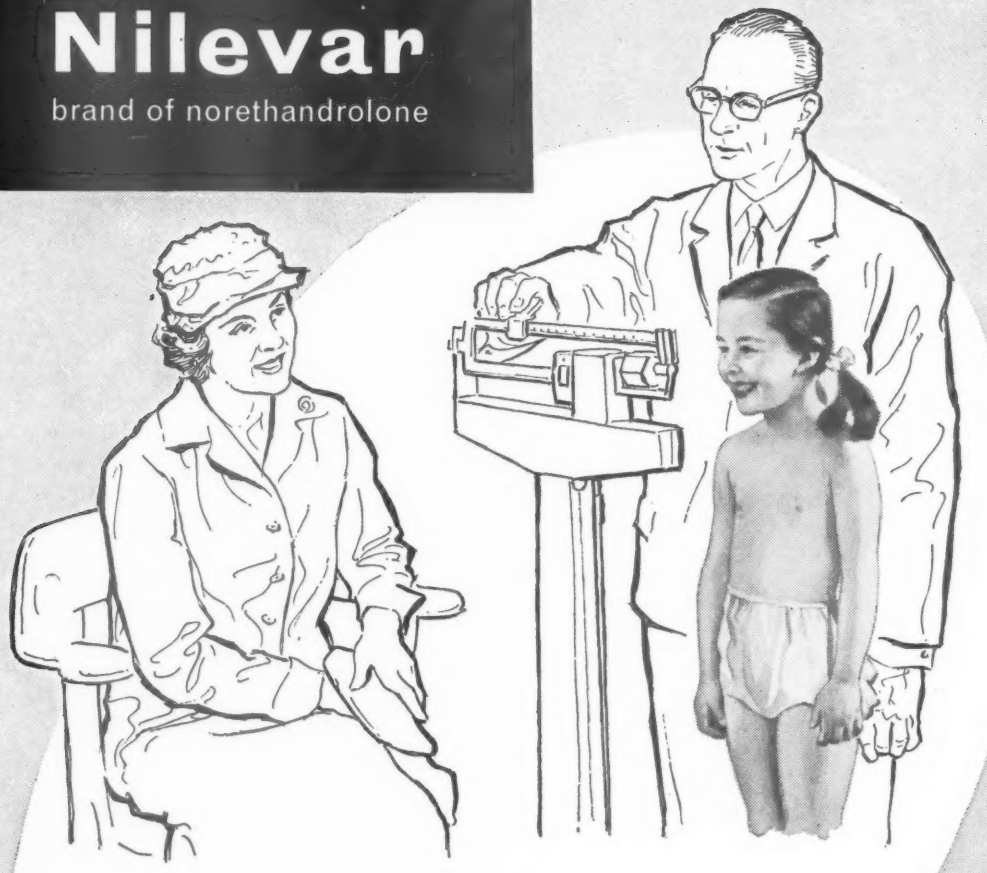

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A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN

PART VI: PHYSICAL DEVELOPMENT IN AGE PERIOD 2 TO 4 YEARS

BY

CECIL MARY DRILLIEN

From the Department of Child Life and Health, University of Edinburgh

(RECEIVED FOR PUBLICATION MAY 30, 1960)

In previous papers in this series (Drillien, 1958a, b; 1959a, b, c) an account has been given of growth and development during the first two years of life of nearly 600 children of different birth weight. These children were born in two Edinburgh maternity hospitals, in the years 1953 to 1955. Approximately one-third of the group were 4½ lb. or less at birth, one-third between 4½ and 5½ lb., and one-third mature controls. The sample includes over 100 pairs of twins. Details of selection and procedure are given elsewhere (Drillien, 1958a). All children in the survey have now reached the age of 4 years, and results are presented here of the analyses of weight and height measurements, in relation to birth weight, sex, whether single or multiple birth, and certain environmental and genetic factors.

Five hundred and ninety-five children were originally selected for study. Of these, 58 (10 of whom died) were lost at or before 2 years. Between 2 and 4 years a further nine children have been lost. Most of the losses have been due to removal from Edinburgh or south Scotland. Only seven children have been lost through refusal of the parents to co-operate, all these before the age of 2 years. At 3 years 92% of surviving children remained in the survey, and at 4 years 90% remained. This wastage rate compares favourably with other longitudinal surveys of this kind. In the Newcastle study (Miller, Court, Walton and Knox, 1960) 78·5% remained at 5 years. Here the major cause of loss was removal from the city, with an excess in families from the two highest social classes. In the Edinburgh survey, children are retained in the sample if they remove to within a radius of about 60 miles, and others have been seen on return to Scotland for holidays. The majority of those lost by removal have emigrated. The social class distribution of those remaining at 4 years does not differ appreciably from that of the original sample. In the national survey of premature and maturely born children (Douglas and Blomfield, 1958) 31% had been lost by 4½ years, most of these due to death; after the exclusion of deaths 94% remained. In the national survey each premature was matched with a maturely born control child, and when either was lost the paired child was also excluded. This is likely to introduce bias if death rates differ in the experimental and control groups, as is the case here. Yearly death rates per 1,000 survivors, between the ages of 1 month and 4½ years, were 14·1% for prematures and 4·4% for controls. Excluding the paired controls has the effect of artificially eliminating these children.

Procedure

Nearly all the children were examined within two weeks of their 3rd and 4th birthdays. Any who were seen later than four weeks after their birthdays have not been included in the subsequent analysis. At 3 years 14 cases were excluded for this reason, and 16 cases at 4 years.

The children have been examined in their own homes. They were weighed in light indoor clothes, without shoes, an appropriate deduction being made for clothes still worn, and measured recumbent, without shoes, on a portable measuring board.

Mean Measurements of Weight and Height

Tables 1-4 give mean weights and heights, mean weight and height increments, and the standard deviations of these means for male and female singletons and twins in four birth weight groups, at ages 1, 2, 3 and 4 years. The means are recorded in British units and their metric equivalents. At

1

TABLE 1: MEAN WEIGHTS AND HEIGHTS OF MALE SINGLETONS AND TWINS AT AGES 1-4 YEARS

Age (yrs)	Birth Weight*	Weight (lb.)	S.D. (oz.)	Weight (kg.)	S.D. (g.)	No. of Cases	Height (in.)	S.D. (in.)	Height (cm.)	S.D. (cm.)	No. of Cases
Male Singletons											
1	1	19·3	6	8·750	182	53					
	2	21·0	5	9·545	127	62					
	3	22·9	8	10·398	236	26					
	4	23·9	7	10·881	191	30					
2	1	24·6	7	11·193	186	52	31·9	0·67	81·1	1·70	52
	2	25·5	5	11·591	136	63	33·1	0·15	84·0	0·37	63
	3	27·4	9	12·472	240	26	34·2	0·58	86·8	1·47	26
	4	28·6	9	12·983	254	30	34·2	0·23	87·4	0·58	27
3	1	28·9	7	13·153	209	49	35·8	0·54	91·0	1·38	49
	2	29·8	6	13·551	159	63	36·5	0·52	92·6	1·31	63
	3	32·1	10	14·602	277	26	37·4	0·84	95·1	2·13	25
	4	33·1	11	15·028	308	28	37·6	0·82	95·5	2·09	27
4	1	33·1	9	15·028	249	45	38·7	1·1	98·4	2·75	45
	2	33·8	7	15·369	195	60	39·3	0·61	99·9	1·55	60
	3	36·6	12	16·619	336	24	40·6	0·96	103·0	2·44	24
	4	37·4	14	17·017	404	29	40·5	0·80	102·8	2·02	29
Male Twins											
1	1	18·5	7	8·409	204	25					
	2	20·4	9	9·290	254	28					
	3	22·6	6	10·284	163	39					
	4	22·8	9	10·369	254	6					
2	1	23·5	8	10·682	240	27	32·4	0·33	82·3	0·85	24
	2	25·6	7	11·648	200	28	33·0	0·24	83·8	0·61	28
	3	27·6	7	12·557	209	39	34·0	0·21	86·3	0·53	38
	4	28·1	18	12·784	500	5	33·4	0·31	84·8	0·80	5
3	1	28·3	11	12·869	304	25	35·8	1·35	91·0	3·44	25
	2	29·7	9	13·466	263	28	36·4	0·84	92·5	2·14	28
	3	32·0	9	14·545	259	36	37·2	0·76	94·6	1·93	36
	4	34·6	11	15·710	308	3	37·3	3·20	94·8	8·18	3
4	1	32·1	12	14·574	349	25	38·5	1·49	97·8	3·78	25
	2	33·3	9	15·114	263	27	39·1	1·01	99·4	2·57	27
	3	35·9	11	16·335	313	36	40·0	0·84	101·6	2·13	36
	4	36·6	4	16·619	953	4	39·7	1·20	100·8	6·24	4

TABLE 2: MEAN WEIGHTS AND HEIGHTS OF FEMALE SINGLETONS AND TWINS AT AGES 1-4 YEARS

Age (yrs)	Birth Weight*	Weight (lb.)	S.D. (oz.)	Weight (kg.)	S.D. (g.)	No. of Cases	Height (in.)	S.D. (in.)	Height (cm.)	S.D. (cm.)	No. of Cases
Female Singletons											
1	1	19·2	7	8·693	191	47					
	2	20·0	7	9·901	186	75					
	3	21·2	7	9·631	186	40					
	4	22·9	10	10·426	281	20					
2	1	24·4	7	11·080	195	42	32·6	0·26	82·7	0·65	42
	2	24·7	6	11·222	168	75	32·8	0·17	83·2	0·43	74
	3	25·9	6	11·761	154	38	33·5	0·21	85·2	0·53	37
	4	27·5	10	12·500	295	19	34·0	0·27	86·4	0·68	19
3	1	28·8	9	13·096	254	44	36·0	0·90	91·5	2·28	44
	2	28·9	7	13·125	186	73	35·9	0·47	91·2	1·20	73
	3	30·5	8	13·864	236	38	36·7	0·72	93·1	1·82	38
	4	32·5	13	14·773	376	19	37·5	1·28	95·2	3·24	19
4	1	32·7	11	14·886	304	44	38·9	1·03	98·7	2·62	42
	2	32·5	8	14·773	218	71	38·7	0·61	98·2	1·56	71
	3	34·4	11	15·623	313	35	39·6	0·89	100·5	2·27	35
	4	37·3	18	16·960	499	19	40·3	1·52	102·4	3·86	19
Female Twins											
1	1	18·1	8	8·239	213	30					
	2	20·0	13	9·091	367	32					
	3	21·4	6	9·716	181	36					
	4	23·7	11	10·767	318	5					
2	1	23·3	8	10·597	227	30	31·8	0·26	80·7	0·65	28
	2	24·4	10	11·080	286	28	32·4	0·28	82·3	0·71	28
	3	25·9	6	11·790	168	33	33·2	0·25	84·4	0·63	32
	4	29·1	7	13·239	191	5	34·4	1·50	87·5	3·70	5
3	1	27·8	11	12·614	313	28	35·3	1·02	89·6	2·58	28
	2	28·1	11	12·756	299	27	35·4	0·92	90·0	2·34	27
	3	30·2	8	13·722	222	33	36·5	0·86	92·8	2·19	33
	4	35·0	25	15·909	699	5	37·8	1·20	95·9	3·10	5
4	1	31·4	13	14·290	358	28	37·8	1·09	96·0	2·77	28
	2	32·1	12	14·602	340	27	38·5	0·89	97·7	2·27	27
	3	34·8	10	15·795	290	33	39·5	0·91	100·5	2·30	33
	4	39·4	36	17·899	1,016	5	41·0	1·36	104·1	3·46	5

* Birth weight, lb. oz. (g.): 1 = 4·8 and under (2,045 g. and under)
2 = 4·9–5·8 (2,046–2,500 g.)
3 = 5·9–7·8 (2,501–3,409 g.)
4 = 7·9 and over (3,410 g. and over)

TABLE 3: MEAN WEIGHT AND HEIGHT INCREMENTS OF MALE SINGLETONS AND TWINS AT AGES 1-4 YEARS

Age (yrs)	Birth Weight	Weight Increment					Height Increment				
		(lb.)	S.D. (oz.)	(kg.)	S.D. (g.)	No. of Cases	(in.)	S.D. (in.)	(cm.)	S.D. (cm.)	No. of Cases
Male Singletons											
1	1	15·7	6	7·121	172	53					
	2	15·9	4	7·212	127	62					
	3	15·9	9	7·212	245	26					
	4	15·4	7	6·985	186	30					
2	1	20·9	7	9·480	186	52	15·3	0·35	38·9	0·90	52
	2	20·4	5	9·253	145	63	14·9	0·19	37·9	0·47	63
	3	20·5	8	9·299	236	26	14·4	0·36	36·5	0·91	26
	4	20·1	9	9·117	245	30	13·9	0·25	35·4	0·63	27
3	1	25·3	7	11·476	200	49	18·9	0·62	48·0	1·58	49
	2	24·7	6	11·204	159	63	18·3	0·57	46·4	1·44	63
	3	25·2	10	11·431	277	26	17·5	1·00	44·8	2·53	25
	4	24·5	10	11·113	281	28	17·1	0·85	43·4	2·16	27
4	1	29·3	9	13·290	259	45	21·7	0·88	55·0	2·23	45
	2	28·6	7	12·973	204	60	21·1	0·63	53·7	1·59	60
	3	29·6	12	13·426	331	24	20·8	1·10	52·7	2·79	24
	4	28·9	13	13·109	367	29	19·8	0·82	50·4	2·09	29
Male Twins											
1	1	14·7	8	6·600	222	25					
	2	15·5	10	7·031	272	28					
	3	16·1	6	7·303	163	39					
	4	15·0	9	6·804	268	6					
2	1	19·5	8	8·845	240	27	15·2	0·28	38·6	0·71	24
	2	20·4	7	9·253	204	28	14·6	0·30	37·0	0·77	28
	3	21·4	8	9·707	222	39	14·5	0·25	36·9	0·63	38
	4	20·3	19	9·208	535	5	13·1	0·42	33·4	1·07	5
3	1	24·3	11	11·022	304	25	18·7	1·57	47·5	3·99	25
	2	24·5	9	11·113	268	28	18·0	0·97	45·7	2·46	28
	3	25·7	9	11·657	254	36	17·8	0·85	45·2	2·16	36
	4	26·9	10	12·202	295	3	17·2	2·79	43·7	7·09	3
4	1	28·0	11	12·701	304	25	21·4	1·60	54·5	4·07	25
	2	28·0	9	12·701	268	27	20·8	1·02	52·7	2·74	27
	3	29·6	10	13·426	295	36	20·4	0·89	51·9	2·27	36
	4	28·7	35	13·018	993	4	19·3	2·50	49·0	6·36	4

TABLE 4: MEAN WEIGHT AND HEIGHT INCREMENTS OF FEMALE SINGLETONS AND TWINS AT AGES 1-4 YEARS

Age (yrs)	Birth Weight	Weight Increment					Height Increment				
		(lb.)	S.D. (oz.)	(kg.)	S.D. (g.)	No. of Cases	(in.)	S.D. (in.)	(cm.)	S.D. (cm.)	No. of Cases
Female Singletons											
1	1	15·5	4	7·031	104	47					
	2	15·2	5	6·895	136	75					
	3	14·4	6	6·532	172	40					
	4	14·9	12	6·759	327	20					
2	1	20·3	11	9·185	308	42	15·6	0·25	39·5	0·64	42
	2	19·6	5	8·890	154	75	14·5	0·18	36·8	0·45	74
	3	19·1	6	8·664	181	38	15·0	0·28	38·0	0·72	37
	4	19·3	10	8·754	281	19	13·7	0·26	34·9	0·66	19
3	1	25·1	9	11·385	245	44	18·9	0·90	48·0	2·28	44
	2	23·8	6	10·795	172	73	17·9	0·61	45·4	1·56	73
	3	24·1	9	10·932	263	38	17·2	0·79	43·7	2·00	38
	4	24·3	13	11·022	367	19	17·1	1·27	43·5	3·22	19
4	1	29·1	10	13·200	295	44	21·8	1·00	55·3	2·55	42
	2	27·4	7	12·428	204	71	20·5	0·62	52·0	1·58	71
	3	27·6	11	12·519	299	35	20·0	0·99	50·9	2·52	35
	4	29·1	17	13·200	481	19	19·9	1·52	50·6	3·87	19
Female Twins											
1	1	14·4	7	6·532	209	30					
	2	15·1	8	6·849	218	32					
	3	15·1	7	6·849	186	36					
	4	15·6	9	7·076	263	5					
2	1	19·4	8	8·800	218	30	15·0	0·26	38·1	0·67	28
	2	19·4	10	8·800	286	28	14·3	0·31	36·3	0·79	28
	3	19·6	6	8·890	163	33	13·7	0·30	34·9	0·77	32
	4	21·3	6	9·662	163	5	14·5	0·37	36·9	0·94	5
3	1	23·9	11	10·841	299	28	18·1	1·19	46·1	3·02	28
	2	23·0	11	10·433	299	27	17·3	1·12	43·9	2·84	27
	3	23·8	7	10·795	209	33	17·0	1·07	43·2	2·72	33
	4	26·9	23	12·202	653	5	17·2	1·12	43·8	2·85	5
4	1	27·6	11	12·519	299	28	21·0	1·20	53·2	3·16	28
	2	27·1	12	12·292	336	27	20·5	1·44	52·0	3·65	27
	3	28·4	10	12·882	272	33	20·1	1·07	50·9	2·73	33
	4	31·3	34	14·175	966	5	20·5	1·13	52·0	2·87	5

each age mean weight is related to birth weight, and the prematurely born show little tendency to overcome their initial weight handicap. In general, the highest weight increments for singletons are recorded for those who were 4½ lb. or less at birth. At ages 3 and 4 the lowest increments are those in the 4½ to 5½ lb. group. This group includes a preponderance of small full-term children, and the significance of this is discussed in a later section. At 4 years there is an excess in mean weight increment for those over 5½ lb. at birth, as compared with those who were 5½ lb. or less, amounting to 5 oz. for boys and 1 oz. for girls. This small difference has no practical or statistical significance. One may say that for the total premature group the singleton is as far behind in actual weight at 4 years as he was at birth.

Amongst twin births there is quite a marked difference in four-year weight increment by birth weight, increment being greater for those over 5½ lb. by 1·5 lb. for boys and 1·4 lb. for girls. This difference is statistically significant ($p < 0{\cdot}02$). For all birth weight groups twins are lighter at 4 years, as compared with singletons, the difference being most marked in those who were 4½ lb. or less at birth. In this group twin boys are 1 lb. lighter than singletons, and twin girls 1·3 lb. lighter.

At 4 years larger weight increments are recorded for boys than girls, amounting to 0·75 lb. for premature and just over 1 lb. for maturely born singletons, and 0·75 lb. for twins of all birth weights. At 6 months the excess male weight increment for singletons was 11 oz. for premature and 18 oz. for maturely born male singletons, and 7 oz. and 14 oz. for premature and maturely born male twins. The difference in weight gain between the sexes at 4 years is almost identical. Falkner (1958) noted that rate of growth was very similar for singleton boys and girls up to the age of 3 years, except for an excess male weight gain in the first three months.

Mean measurements of height show that at 4 years of age the prematurely born are still shorter than the mature controls by between 1 and 1½ inches. However, in all groups of male and female singletons and twins, height increments are related inversely to size at birth. There appears to be a definite tendency for those smallest at birth to reduce their initial height handicap more quickly than their weight handicap, and at 4 years they tend to be underweight, as compared with mature controls of like height.

Height increments are approximately equal for boys and girls, being 21·4 and 21·0 in. for male and female premature singletons at 4 years, and 20·3 and 20·0 in. for male and female mature singletons, giving an excess height increment of 1 in. in the premature group. Likewise, increments for male and female twins who were 5½ lb. or less at birth are 21·1 and 20·7 in. respectively and for twins over 5½ lb., 20·3 and 20·1 inches.

At 4 years boys are approximately 0·5 in. taller than girls, in both premature and mature groups, as they were at birth.

The Effect of Environment on Rate of Growth

The analysis of weight and height measurements at 2 years showed that rate of growth was related to such environmental factors as maternal efficiency, diet and illness, the effect being more marked in those who were prematurely born than in mature children from similar types of home.

Maternal Care. Tables 5-8 show mean weight and height increments at 4 years for singletons and twins in three birth weight groups by the estimated efficiency of their mothers. Tables 5 and 6 also give the proportion of mothers in each birth weight group who were considered to be giving the child good or very good (1), average (2), or poor (3) care. These assessments are entirely subjective, but are considered to be valid comparisons of different standards of care within the group, as the assessments have all been made by the same observer within the child's own home. Where maternal efficiency is graded 1, the children are well fed, adequately clothed, sensibly handled and enjoy a regular routine. The houses are clean and reasonably well equipped. Cases graded 2 are those where maternal care is unsatisfactory in some respects, but not markedly so, the cause usually to be found in circumstances outside the mother's control, such as inadequate housekeeping allowance, a large family of young children, an unsatisfactory husband, poor housing or poor maternal health. Where maternal care is graded 3 the home environment is obviously unsatisfactory as regards diet, cleanliness and routine. In many cases these mothers are of limited intelligence, and receive little support from their husbands.

Among singletons standards of care were markedly higher in the mature control group. Three-quarters of these mothers were considered to be giving good care, compared with about one half in the two premature groups. The average standard of care was lower for twins in all groups, and shows little difference by birth weight. The reason appears to be two-fold. Some mothers who could manage a single baby satisfactorily are less able to cope with twins. This was felt to be the case especially with young mothers, following a first or second pregnancy. There was also an excess of older mothers

TABLE 5

MEAN FOUR-YEAR WEIGHT INCREMENTS BY MATERNAL CARE (SINGLETONS)

Maternal Care	Birth Weight A (4 lb. 8 oz. and under)		Birth Weight B (4 lb. 9 oz.–5 lb. 8 oz.)		Birth Weight C (5 lb. 9 oz. and over)		Difference A–C	
	Receiving Different Care (%)	Weight Increment lb. oz.	Receiving Different Care (%)	Weight Increment lb. oz.	Receiving Different Care (%)	Weight Increment lb. oz.	lb.	oz.
1	56·2	30 2	51·9	28 11	73·8	29 6	+	12
2	29·2	28 6	26·0	27 0	14·1	26 9	+1	13
3	14·6	27 2	22·1	26 3	12·1	27 10	−	8
Difference 1–3		3 0		2 8		1 12		
No. of Cases	89		131		109			

TABLE 6

MEAN FOUR-YEAR WEIGHT INCREMENTS BY MATERNAL CARE (TWINS)

Maternal Care	Birth Weight A (4 lb. 8 oz. and under)		Birth Weight B (4 lb. 9 oz.–5 lb. 8 oz.)		Birth Weight C (5 lb. 9 oz. and over)		Difference A–C	
	Receiving Different Care (%)	Weight Increment lb. oz.	Receiving Different Care (%)	Weight Increment lb. oz.	Receiving Different Care (%)	Weight Increment lb. oz.	lb.	oz.
1	49·0	29 5	44·5	28 14	51·3	29 4	+	1
2	20·8	27 6	33·3	26 5	17·9	30 14	−3	8
3	30·2	25 10	22·2	26 13	30·8	27 15	−2	5
Difference 1–3		3 11		2 1		1 5		
No. of Cases	53		54		78			

TABLE 7

MEAN FOUR-YEAR HEIGHT INCREMENTS BY MATERNAL CARE (SINGLETONS)

Maternal Care	Mean Height Increment (in.) Birth Weight A 4 lb. 8 oz. and under	B 4 lb. 9 oz.–5 lb. 8 oz.	C 5 lb. 9 oz. and over	Difference A-C
1	21·9	21·2	20·5	1·4
2	22·0	20·5	19·5	2·5
3	20·7	20·1	19·1	1·6
Difference 1–3 ..	1·2	1·1	1·4	

TABLE 8

MEAN FOUR-YEAR HEIGHT INCREMENTS BY MATERNAL CARE (TWINS)

Maternal Care	Mean Height Increment (in.) Birth Weight A 4 lb. 8 oz. and under	B 4 lb. 9 oz.–5 lb. 8 oz.	C 5 lb. 9 oz. and over	Difference A–C
1	21·9	21·3	20·5	1·4
2	21·6	20·3	20·8	0·8
3	19·7	19·7	19·5	0·2
Difference 1–3 ..	2·2	1·6	1·0	

with four or more other children in the twins' group, as compared with singletons. This was particularly so in those twins over 5½ lb. at birth, and accounts for the lower average standard of care of maturely born twins. It was shown in a previous paper (Prillien, 1959b) that in general maternal care deteriorated with increasing size of family.

Mean weight increments of singletons decrease with declining maternal standards in all birth weight groups, the effect being most noticeable in those smallest at birth. There is a difference of 3 lb. in mean four-year weight increment between those children receiving the best and worst care who were smallest at birth, compared with 1¾ lb. in the mature control group.

Weight increments are biggest for those who were 4½ lb. or less at birth, except for those receiving the poorest care, and tend to be smallest in the 4½-5½ lb. birth weight group.

In the twin group lower mean weight increments are also recorded for less satisfactory care, especially in those who were 4½ lb. or less at birth. Here the difference between those receiving the best and worst care is 3¾ lb. Only in the group receiving the best

care are increments highest for those smallest at birth. Increments are approximately equal for twins and singletons receiving like care whose birth weights were over 4½ lb., but in the smallest birth weight group increments for twins are less for all grades of care.

Mean height increments are also related to maternal care for both singletons and twins, the effect being most marked in those twins smallest at birth. Here there is a difference of 2·2 in. between those receiving the best and worst care. In all maternal care groups mean height increment increases with decreasing birth weight, this being more noticeable for singletons.

From these figures it appears that weight and height at 4 years are related both to birth weight and maternal care. The effect of poor maternal care is most marked in those who were smallest at birth, and affects twins more than singletons. Small prematurely born children receiving poor care tend to be not only shorter and lighter, but also underweight for their height.

Incidence of Illness. The incidence of medical illness during the third and fourth years of life has been scored to take into account the number of disease incidents and the severity of these episodes. The reporting of illness is not thought to be as accurate during this age period as it was in the first two years of life. In most cases the interval between visits has been 12 months instead of six. There is probably considerable under-reporting in the poorest homes, especially of less serious conditions. After the age of 2 the poorer types of mothers are more likely to ignore such episodes as sore throats, diarrhoea, and feverish colds, whereas the mother from a superior working class or middle class home continues to seek medical aid. Incidence of illness has been graded as (1) little or none, (2) some, and (3) more frequent.

Tables 9 and 10 give mean weight and height increments at 4 years for these illness grades, by birth weight, in singletons and twins. The reported incidence of illness was approximately the same for singletons of all birth weights and twins over 4½ lb. at birth. The smallest twins had a significantly higher incidence of frequent illness, being more than twice as high (36%) than for singletons of like birth weight (17%). Smaller weight and height increments are recorded for singletons who were 4½ lb. or less at birth and all birth weight groups of twins, as incidence of illness increases. In singleton groups over 4½ lb. at birth recorded increments at 4 years were higher for those who were said to have had more illness, though the differences between illness grades are not significant.

Incidence of illness is correlated with maternal care, although not to the same extent as in the first two years of life, and it is likely that the apparent effect of illness is a reflection of the child's total environment. Compared with the age period from birth to 2 years, fewer children suffered constant ill health.

In the Newcastle study (Miller *et al.*, 1960) a significant correlation was found between stature at 3 years and the incidence of severe respiratory infections, although this was practically limited to children having four or more illnesses. These authors point out that the incidence of severe respiratory disease is itself correlated strongly with adverse environmental conditions, and suggest that a common factor is likely to explain both the small stature and increased frequency of illness.

In the two-year growth analysis (Drillien, 1958b) it was shown that prematurely born singletons from the best environment had very nearly caught up, both in weight and height, with the total mature group by 2 years, but twins who were 4½ lb. or less at birth were still substantially behind those over this birth weight in both weight and height. Tables 11 and 12 give mean weights and heights and weight and height increments at 4 years for 'selected' prematures (i.e. those receiving the best care and having no more than a moderate amount of illness), as compared with 'selected' maturely born children and the total control group, for singletons and twins. The mean height of the mothers is also given. At 4 years the 'selected' prematurely born are still lighter and shorter than the maturely born. The difference in weight of singletons is greater than at 2 years. The smallest prematures are now 2 lb. lighter than the mature controls, compared with 14 oz. at 2 years. Those between 4½ and 5½ lb., are nearly 3 lb. lighter than the matures. It is noticeable that the average height of mothers in this group is approximately 1 in. less than for the other two groups. In a previous study of the social aetiology of prematurity (Drillien, 1957) it was shown that, whereas, in the mature control group, height of mother was positively correlated with weight of baby, in the premature group the relationship was reversed. It was concluded that babies classified as premature on a weight basis were a mixture of two categories, early and small full-term. The mothers of the latter were significantly shorter than those with early babies. In height the prematurely born are about 1 in. shorter than the control group, which is rather more than at 2 years. The differences at 4 years between twins who were

TABLE 9

MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS (SINGLETONS) BY FREQUENCY OF ILLNESS

Illness Grade	Birth Weight					
	4 lb. 8 oz. and under		4 lb. 9 oz.–5 lb. 8 oz.		5 lb. 9 oz. and over	
	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)
1	30 9	21·5	27 7	20·8	28 7	20·2
2	28 14	21·6	27 15	20·7	28 1	19·9
3	27 1	20·9	28 13	20·9	29 9	20·5
Difference 1–3	3 8	0·6	−1 6	−0·1	−1 2	−0·3

TABLE 10

MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS (TWINS) BY FREQUENCY OF ILLNESS

Illness Grade	Birth Weight					
	4 lb. 8 oz. and under		4 lb. 9 oz.–5 lb. 8 oz.		5 lb. 9 oz. and over	
	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)
1	29 4	22·2	28 4	21·1	29 14	20·4
2	28 10	21·8	27 12	20·9	29 1	20·4
3	25 10	19·6	25 12	19·1	28 13	19·8
Difference 1–3	3 10	2·6	2 8	2·0	1 1	0·6

TABLE 11

MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS FOR 'SELECTED' PREMATURES AND MATURE CONTROLS (SINGLETONS)

Mean	Selected			Total Mature
	Birth Weight			
	4 lb. 8 oz. and under	4 lb. 9 oz.–5 lb. 8 oz.	5 lb. 9 oz. and over	
Birth weight ..	3·8	5·2	7·6	7·6
Weight at 4 years ..	34·3	33·6	36·6	36·2
Weight increment ..	30·5	28·4	29·0	28·6
Height at 4 years (in.)	39·4	39·4	40·4	40·2
Height, mothers (in.)	63·3	62·2	63·4	63·0
No. of cases ..	42	55	69	107

TABLE 12

MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS FOR 'SELECTED' PREMATURES AND MATURE CONTROLS (TWINS)

Mean	Selected			Total Mature
	Birth Weight			
	4 lb. 8 oz. and under	4 lb. 9 oz.–5 lb. 8 oz.	5 lb. 9 oz. and over	
Birth weight ..	3·9	5·2	6·8	6·6
Weight at 4 years ..	33·5	33·9	36·2	35·7
Weight increase ..	29·6	28·7	29·4	29·1
Height at 4 years (in.)	39·2	39·4	40·3	39·9
Height, Mothers (in.)	62·9	63·7	63·9	63·5
No. of cases ..	23	23	35	78

under or over 5½ lb. at birth are approximately the same as for singletons, although at 2 years the smallest twins were much further behind in weight and height than singletons of like birth weight.

It appears that at 4 years birth weight still has an effect on stature, and prematurely born children from the best homes are still smaller than the naturely born, even when height of mother is taken into account. Twins have overcome their disability, as compared with singletons; the smaller size of those twins who were 4½ lb. or less at birth may be attributed to the fact that the average height of the mother happens to be lower in this twin group.

The Effect of Gestational Period on Rate of Growth

At 2 years no significant correlation was found between length of gestation and weight and height increments. It might be expected that post-natal growth would be slower in those small babies born at or near term, often to mothers of small stature, but this was not demonstrable at 2 years. Douglas and Mogford (1953) failed to demonstrate any independent effect of gestation time on 4-year weight and height. However, in the Edinburgh study obvious differences had appeared by the age of 4, as shown in Table 13. In the birth weight group

TABLE 13

MEAN FOUR-YEAR WEIGHTS AND HEIGHTS FOR CHILDREN 5½ LB. OR LESS AT BIRTH, BY GESTATION PERIOD

Mean	Gestation (weeks)	Birth weight	
		4 lb. 8 oz. and under	4 lb. 9 oz.-5 lb. 8 oz.
Weight at 4 years ..	37 or less	34·5	34·9
	38 or more	33·8	32·5
Height at 4 years (in.) ..	37 or less	39·2	39·7
	38 or more	39·6	39·0
Height, mothers (in.) ..	37 or less	63·3	62·2
	38 or more	63·4	62·2

4½ lb. or less, 83% of mothers gave the gestation time as being 37 weeks or less. In the group 4½-5½ lb. the estimated gestation time was 38 weeks or more in 55% of cases. These small full-term babies were 2½ lb. lighter at 4 years and 0·75 in. shorter than babies of like birth weight whose estimated gestation time was less than 38 weeks.

The Effect of Parental Heights

In the 2-year growth analysis it was found that rate of growth was affected not only by environmental factors but also by genetic factors, as deduced from parental heights. Genetic and environmental factors were intercorrelated to quite a high degree, and the technique of correlation and regression analysis was used to disentangle the relative contribution of different factors. It was then found that genetic and environmental factors were of approximately equal importance in their influence on growth, whether measured by height or weight increment at 2 years.

Table 14 gives first order correlation coefficients between weight and height increments at 4 years and maternal care, and between these increments and maternal height, for singletons and twins in different birth weight groups, with the levels of significance of these coefficients.

In general, the correlation coefficients between rate of growth and the representative environmental and genetic factors are higher at 4 years than at 2 years, the highest correlations being recorded for those who were smallest at birth, and being higher for twins who were 5½ lb. or less at birth than for singletons of like birth weight. As at 2 years, correlations between increments and maternal height are rather higher than those between increments and maternal care. However, it should be remembered that maternal heights are themselves environmentally determined in part. Baird and Illsley (1953) have pointed out that a mother's height and physical grade are directly associated with her pre-marital environment. Baird (1959) also demonstrated an association between small stature and under-average intelligence in mothers.

Table 15 gives the proportion of mothers who were short, medium, and tall in each maternal care group. In the group giving the poorest care more than half the mothers were 5 ft. 1 in. or less compared with less than a quarter of small mothers in the best care group. Table 16 gives mean weight and height increments at 4 years for children born to short, medium, and tall mothers in the three care groups, and demonstrates how rate of growth increases with height of mother, for all grades of care, and decreases with declining standards of care, for all heights of mother. The differences are greater by height of mother, but this does not neces-

TABLE 14

CORRELATION COEFFICIENTS BETWEEN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS AND MATERNAL CARE AND MATERNAL HEIGHT, FOR SINGLETONS AND TWINS

	Birth Weight lb. oz.	Correlation Coefficients Between Weight Increment and:			
		Maternal Grade	p	Maternal Height	p
Singletons	4·8 and under	0·3045	<0·01	0·5215	<0·001
	4·9–5·8	0·1905	<0·05	0·3768	<0·001
	5·9 and over	0·2144	<0·05	0·1808	not significant
Twins	4·8 and under	0·4483	<0·001	0·4517	<0·001
	4·9–5·8	0·3028	<0·05	0·4919	<0·001
	5·9 and over	0·1411	not significant	0·3661	<0·01
	Birth Weight lb. oz.	Correlation Coefficients Between Height Increment and:			
		Maternal Grade	p	Maternal Height	p
Singletons	4·8 and under	0·2504	<0·02	0·5595	<0·001
	4·9–5·8	0·2939	<0·001	0·2627	<0·01
	5·9 and over	0·1970	<0·05	0·3688	<0·001
Twins	4·8 and under	0·4461	<0·001	0·4561	<0·001
	4·9–5·8	0·3742	<0·01	0·2848	<0·05
	5·9 and over	0·2698	<0·02	0·2520	<0·02

TABLE 15
MATERNAL CARE BY HEIGHT OF MOTHER

Maternal Care	Height of Mother						Total	
	5 ft. 1 in. and under		5 ft. 2 in. and 5 ft. 3 in.		5 ft. 4 in. and over			
	No.	%	No.	%	No.	%	No.	%
1	67	23·5	88	30·9	130	45·6	285	100·0
2	46	40·0	39	33·9	30	26·1	115	100·0
3	56	54·4	23	22·3	24	23·3	103	100·0

TABLE 16
MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS BY MATERNAL CARE AND MATERNAL HEIGHT

Maternal Care	Maternal Height						Difference C–A	
	A 5 ft. 1 in. and under		B 5 ft. 2 in.–5 ft. 3 in.		C 5 ft. 4 in. and over			
	Mean		Mean		Mean			
	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)
1	27 10	20·3	29 6	21·0	30 3	21·7	2 9	1·4
2	26 2	20·3	28 5	20·8	28 12	21·6	2 10	1·3
3	25 13	19·3	27 15	20·3	28 8	20·4	2 11	1·1
Difference 1–3	1 13	1·0	1 7	0·7	1 11	1·3		

sarily mean that rate of growth is affected more by parental height than by environment. Height can be measured accurately, whereas even the best estimate of maternal care must be considerably less accurate.

Heights of fathers show similar correlations with rate of growth, although these tend to be lower than those for maternal height. This would be expected as the fathers were not measured but merely asked to state their height, and these estimates are likely to be less accurate. It was shown in the previous paper on growth that father's height is quite highly correlated with mother's height, and also with maternal efficiency.

The Effect of Feeding Problems on Rate of Growth

Reference has been made in a previous paper (Drillien, 1959c) to feeding problems in the first two years of life, defined as refusal to eat or excessive faddiness, lasting for three to six months or longer. No difference could be demonstrated in weight or height increments at 2 years between those who had or had not exhibited feeding problems, even when the refusal to eat had been prolonged.

During the age period 2 to 4 years about 16% of the total group exhibited feeding problems lasting for six months or longer (the incidence was 15% during the first two years of life). At 4 years some obvious difference was found, particularly in weight increment, between those who had or had not exhibited feeding problems as shown in Table 17. Mean increments are given, by maternal grade, as the incidence varies with grade, being highest with those mothers giving the best maternal care. The question of feeding problems will be considered more fully in a later paper.

Summary

A statistical analysis is presented of a study of physical growth in the age period 2 to 4 years, in a group of 500 children of varying birth weight. The following conclusions were reached:

At 4 years mean weights for the total premature group and mature group are closely related to birth weight for singleton births.

In the premature group the highest weight increments are recorded for those who were smallest at birth, and the lowest for those who were between $4\frac{1}{2}$ and $5\frac{1}{2}$ lb.

TABLE 17
MEAN FOUR-YEAR WEIGHT AND HEIGHT INCREMENTS FOR THOSE WITH AND WITHOUT FOOD FADS

Maternal Grade	Food Fads			
	With		Without	
	Weight Increment lb. oz.	Height Increment (in.)	Weight Increment lb. oz.	Height Increment (in.)
1	27 2	20·5	29 9	21·3
2	27 8	20·8	27 15	21·6
3	25 12	20·3	27 3	19·8

For twin births significantly smaller weight increments are recorded for those less than 5½ lb. at birth, compared with those over this weight. In all birth weight groups lower increments are recorded for twins than for singletons.

Larger weight increments are recorded for both singleton and twin boys, as compared with girls. This is largely accounted for by excess male weight increments in the first six months of life.

At 4 years the prematurely born are still between 1 and 1½ in. shorter than the mature controls, although increments for all birth weight groups of singletons and twins are inversely related to birth weight. Height increments are approximately equal for boys and girls. At 4 years the prematurely born tend to be lighter and shorter than the controls, and also underweight for their height.

The following different factors have been shown to have an effect on rate of growth:

(*a*) Maternal care. Lower weight and height increments are recorded in all birth weight groups as standards of maternal care deteriorate. The effect of poor care is most marked on those who were smallest at birth and on twins of all birth weights.

(*b*) Morbidity. Smaller increments are recorded with increasing frequency of illness for singletons who were less than 4½ lb. at birth and for twins. Recorded incidence of illness is considered to be a less sensitive index of total environment during the 2 to 4 year age period than it was during the first two years of life. Those prematures receiving the best care and having little illness show larger growth increments, but are still behind the mature controls at 4 years.

(*c*) Gestation period. Those children of birth weight 4½-5½ lb. who were born at or near term were both shorter and lighter at 4 years than children of like birth weight who were premature by gestation as well as by weight. The average height of mother was 1 in. less for children between 4½ and 5½ lb. than for children below and above this birth weight, smaller mothers being more likely to have small babies at term.

(*d*) Parental height. Rates of growth are significantly correlated with parental heights, as well as with maternal care. Environmental and genetic factors are considered to be of about equal importance in their effect on rate of growth.

(*e*) Feeding problems. Prolonged feeding problems during the age period 2 to 4 years appeared to have a definite effect on weight and a lesser effect on height.

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DISORDERS OF SPOKEN LANGUAGE IN YOUNG CHILDREN*

BY

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A number of papers by British authors concerning defects of speech in childhood have recently appeared, notably those of Worster-Drought (1957), to whom all workers in this field owe an outstanding debt, Morley, Court and Miller (1955), Walker and Languth (1956) and Ingram (1959). This paper is concerned with disorders of spoken language in young children.

Definition of Terms

The relevant terminology is confused. In a previous paper (Sheridan, 1959), I offered my own definitions. *Language* is the symbolization of thought in speech, gesture or writing for the purpose of interpersonal communication. *Speech* is the use of systematized vocalizations to express verbal symbols or words. *Hearing* is the reception of sound by the ear and its transmission to the primary auditory area of the cortex. *Listening* is the act of paying attention to the sounds received with the object of interpreting their meaning. *Interpretation* of spoken language depends upon previous *learning*, that is upon the gradual building up of an efficient memory register, to which incoming words can be referred for matching, i.e. *recognition*, and from which needed words can be summoned at will, i.e. *recall*.

Between infants and their mothers a prelinguistic interpersonal communication can be seen which expresses itself in clinging or nestling, in resistive stiffening or furious bodily activity and in unorganized but emotion-charged vocalizations. It is concerned with the direct expression of basic feelings and needs. Later the non-speaking toddler pulls his mother where he wishes her to go, places her hand on an object he desires, points urgently with his finger, smiles, strokes her face caressingly, or throws a tantrum. This primitive form of communication deserves closer study than it has yet received, because when symbolic language fails him the child must resort to it in order to maintain contact with his fellow beings.

Spoken Language

Spoken language implies communication between two brains, or rather two minds. Without entering into discussion concerning the age-old problem of the relation of brain to mind, it can be agreed that mental processes are in some way mediated in the brain. The brain also controls the functional activity of the organs which produce sounds of speech and those which receive sounds made by other people. The function of the brain with regard to spoken language is, therefore, threefold, to *receive*, to *interpret* and to *express*.

Reception depends primarily upon hearing. Unlike the eye, the ear can never 'close down', nor has it any power of selection, but must transmit to the first auditory station in the temporal lobe, through a complicated chain of connexions, whatever medley of sounds is received by the cochlea. From then onwards the mind takes charge. Having decided to listen it proceeds to select the significant or 'foreground' speech elements from the general background of noise, arranges them in orderly groups and finally in the light of intellect and the warmth of emotion interprets their meaning. *Interpretation* depends upon many stored memories not only of the verbal symbols themselves and of the people, objects, activities and trains of thought which they represent, but also of the countless emotions which invest them. As we go through life, every spoken word adds to its fundamental of meaning many overtones of implication. *Expression* is inaugurated by the mind's decision to reply, after which comes the marshalling of relevant ideas and their formulation in language, then the appropriate kinaesthetic assembly, and finally, the motor impulse which puts the required muscles in action to produce results in time, tune and stress. The process is not yet over, however, because as the listener

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receives his message, the speaker simultaneously receives a feed-back into his own central nervous system of a host of stimuli, auditory, vibratory, kinaesthetic, visual, emotional and thought-productive.

Whether or not these mental steps have neurological equivalents, we know from experience that delay or blocking can occur at any one of these levels as a result of functional preoccupation or structural disablement. The received patterns of vocal sounds may be imperfect; willingness to listen may be absent; ability to comprehend may have been lost and so on.

In their recent book, *Speech and Brain-mechanisms*, Penfield and Roberts (1959) have described three regions in the cortex of the dominant hemisphere (usually the left) which they have outlined with electrodes, and which they believe to be concerned with 'ideational speech'. They consider that the 'interpretative cortex' is adjacent to the 3rd or posterior of these speech areas, i.e. is situated in the temporal and inferior parietal regions. They further report:

> 'In a child a major lesion of the posterior speech cortex would produce a transfer of the whole speech mechanism to the opposite hemisphere. Examples of completely successful transfer of speech mechanisms from the left to the right hemisphere of children under three or four years of age are numerous. The upper age limit is not certain . . .'

and, of great interest to those concerned with the special learning difficulties of brain-injured children, they consider the lesions of the corresponding area in the non-dominant hemisphere are associated with 'loss of awareness of the body scheme and of the spatial relationships around him'.

The Acquisition of Spoken Language

The normal acquisition in early childhood of all the biologically determined skills, i.e. locomotion, manipulation, visual discrimination, listening, speaking and social adjustment, depends upon timely opportunity to explore, experiment with and learn to understand the world around him, and to realize how he relates to other people. Upon these spontaneously acquired skills the later attainment of all voluntarily acquired expertise depends. The child instinctively recognizes this. During every moment of his waking day he is impelled to practise and improve his techniques. If, through congenital disability or environmental deprivation, the normal methods of learning and communication are not available to him, he must substitute whatever means are open to him or fail to develop his personality and his intellect.

This biological learning appears to reach its zenith in the first two or three years of life, concurrently with the rapid growth and maturation of the brain, and gradually tapers off by the age of 6 or 7 years, after which habits of functioning appear to be firmly fixed.

Richter (1959) has offered biochemical evidence. He describes a gradual change from one metabolic pattern to another as the 'metabolism of growth' is replaced by the metabolism of mature functioning.

> 'There are critical periods during which in the C.N.S. new enzymes appear, increase in activity and later decline . . . The normal development of nerve cells appears to depend on their receiving a sufficient amount of physiological stimulation during growth.'

Ritchie Russell (1959) has described the acquisition of language in neurological terms.

> 'It is clear that the method first used in early childhood will probably persist throughout life so that the early months of life are the most important for the planning of the brain mechanisms. Further, the neuronal patterns used to learn a word in early childhood will probably be the same as those used in old age.'

Although every child proceeds at his own pace, he must travel from one stage of development to the next by the same stepping-stones. The sensory stimuli from which the child learns are highly complex. They are composed of a dominant sensation and several supplementary ones. For instance, in learning a spoken word the child not only hears it but sees it on his mother's lips and when he is held in her arms feels the vibration of its vocal resonance. He also hears the accompanying cadences of her voice and sees the expression on her face. The child with impaired hearing must rely more heavily than does the normal child upon these supplementary clues.

The reasons for delay or failure in the development of spoken language are not easy to sort out. My own classification is a broad one but even so there is considerable overlapping. Nevertheless, I have found it useful in history-taking and in hopefully guiding treatment towards the next developmental stepping-stone:

Lack of opportunity to learn;
Impaired hearing;
Low intelligence;
Delayed maturation of the central nervous system;
Brain injury;
Psychogenic disorders;
Motor dysfunctions;
Lesions of the peripheral speech organs.

This paper discusses some aspects of faulty reception and interpretation.

Opportunity to Learn. The first of our duties to the growing mind is to provide it with stimulation. The normal baby reacts reflexly to sounds from birth. He hears, but cannot yet listen. His brain is potentially conscious but has everything to learn. Within a few weeks he shows signs of awareness of the person who takes care of him. The world he perceives gradually expands in space and in time, so that, at first capable of paying only momentary heed to happenings within a few inches of his eyes and ears, he is soon able to bestow prolonged and selective attention on objects and events within several feet. Literally he learns to feel, hear and speak on his mother's knee. He comes to associate the touch of her hands, the sight of her face, and the cadences of her voice with the comfort she brings him. At 3 months his immediate response to the near-by human face is to smile, activate and vocalize with pleasure. As Rheingold, Gewirtz and Ross (1959) have shown, these vocalizations are reinforced or extinguished according to the vocal response of the adult. During the first year of life the child receives continual auditory stimulation close to his ear, at high decibel level, in words which are addressed personally to him, and which concern events which affect him directly in the here and now. At the same time he is given strong encouragement to vocalize in return. This intensive individual coaching in the mother-tongue must be given at mother-distance and in the critical period if the child is to acquire fluency in the use of spoken language, otherwise the difficulties of learning to hear and speak are increased not only by diminution of sensory stimulus in time and space, but also by attenuation of emotional rapport. The emotional messages of speech depend upon countless delicate variations of vocal tune and stress. Before the advent of hearing aids, deaf children can have had little conception of the emotional overtones accompanying vocal utterance.

Impaired Hearing. The child speaks as he hears. Speech sounds in common with other varieties of sound possess attributes of pitch, intensity and duration. The human ear is capable of hearing about 10 octaves in pitch. The speech range covers some $7\frac{1}{2}$ octaves from about 100 to 10,000 cycles per second. The frequencies below 1,200 provide most of the energy, resonance and emotional colour of speech, while those above 1,200 cycles are concerned mainly with its intelligibility (Fry, 1957). The chief characteristic components of the vowel sounds are in the lower and middle speech frequencies, the sound */oo/* being the lowest in pitch and the sound */ee/* the highest. The chief components of the consonant sounds are in the middle and high frequencies. The fundamental notes of the nasal sounds */m/n/ng* border on the low frequencies, the continuants */r/l/w/y* are somewhat higher in pitch, the plosives */d/g/t/k* still higher and the fricatures */v/f/th* highest of all. The fundamental vowel pitch of a woman's voice is about an octave higher than a man's. Children's voices are still higher.

Vowel sounds possess the strongest decibel intensity as well as being lowest in pitch and are therefore responsible for the carrying power of speech. The consonants are weaker in intensity but more distinctive in character and are therefore chiefly responsible for intelligibility. The average speaker's voice varies about 30 decibels in intensity between the vowel sound */aw/* which is the strongest and the voiceless consonant */th/* which is the weakest phonetic unit.

The ability to comprehend spoken language therefore necessitates the capacity to hear and interpret a sequence of complicated sounds which vary rapidly by $7\frac{1}{2}$ octaves in pitch and 30 decibels in intensity, and of which the individual units endure only a fraction of a second. It will be obvious that impaired hearing over any part of the speech range, and particularly over the high (consonant-carrying) tones, will lead to delay in the development of speech. Severe loss over the middle and lower frequencies will prevent its spontaneous acquisition altogether. The danger of wrongfully deeming children with impaired hearing mentally retarded must never be forgotten (Sheridan, 1944). Provided the interpretative faculties are intact the young child can make excellent use of a very imperfect field of hearing, but only if he is given expert auditory training, and an efficient hearing aid, in the critical period (Whetnall, 1956, 1958; Ling, 1959). The importance of following up all infants 'at risk', and of early diagnosis, cannot therefore be overstressed (Ballantyne, 1959). The need to compensate for the period of auditory deprivation previous to diagnosis must always be explained to the parents. Otherwise they will be disappointed and perhaps fail to persevere because the child does not begin to speak immediately he is fitted with an aid.

It will be obvious that the deaf child's difficulties are enormously increased if his disability is associated with a defect of central auditory perception. Such cases are fortunately rare although so-called 'oral failures' may be found in most schools for the

deaf. But when it is established that a child is incapable of associating spoken words with meaning he must be given alternative methods of communication, e.g. by writing, finger-spelling or gesture.

Mental Retardation. Mentally backward children are always late in acquiring spoken language. Their infantile vocalizations may also be delayed and are usually meagre in quantity, although they are normally inflected. When inferior genetic endowment is complicated by impaired hearing or organic brain lesions, no matter how minor in degree, language disability is seriously increased. Even when these children possess normal hearing, if they have acquired locomotion before they have had time to store their slow minds with the requisite auditory memories at mother-distance, they must be afforded further opportunities to learn. This implies patient, individual language-training by affectionate and understanding adults using simple words, at close quarters and in homely situations. Otherwise they are denied the possibility of fully developing what faculties they possess. The young mentally handicapped child presents a challenge to the skill and compassion of paediatricians in hospital and public health alike. Too many of these unfortunate children, who could be cared for and trained in the community if more attention were devoted to their problems, and to their parents' difficulties, are at a tender age still referred for admission to large residential institutions.

The speech of young educationally sub-normal children is usually defective, and their language always impoverished. In the past speech therapists were understandably reluctant to accept them for treatment. Many of those who are now willing to undertake responsibility for training them have little previous experience with retarded children and, working unguided and in isolation, tend to expend their energies in speech correction rather than in language development. Renfrew (1959) has made a study of the subject and in a recent valuable paper describes methods of treatment. More vigorous medical and psychological research into the whole problem is needed.

The 'Developmental Aphasias'. In the next group of children delay in acquisition of spoken language is thought to be due to a maturational lag in that part of the central nervous system which deals with span of auditory attention and with language formulation. These late talkers are usually boys, who are normally developed in other respects. Their hearing is good and on performance tests they show average intelligence. They comprehend what is said to them, especially when short, simple sentences are used, but in reply they use only single words or fragmentary phrases helped out with gestures. They are often shy because they realize their social disability but they are friendly and co-operative once their confidence is won. There is frequently a family history of delayed speech. They usually begin to talk at about 3½-4 years of age and then rapidly catch up with their contemporaries, without any apparent damage to their personality or to their ultimate scholastic achievement.

More complex forms of this 'developmental aphasia' or dysphasia sometimes occur. Although they are rare, cases crop up in the experience of every paediatrician and otologist. These children show no auditory loss for faint noises or pure tones, and their intelligence on performance tests may be average, but they are slow to attach meaning to everyday sounds, and particularly to spoken words. Their speech, when it eventually appears at about 3½ to 5 years, is often severely defective in articulation and syntax. They rarely become fluent conversationalists. Some show slight motor clumsiness. Many have special learning difficulties with regard to reading, writing, spelling and drawing. The condition (or group of conditions) has been variously described as auditory imperception, word deafness, strephosymbolia or dyslexia according to the chief presenting symptom. There is sometimes a history of difficult birth, serious illness in the first years of life or frank head injury, so that it is tempting to hypothesize neurological damage rather than developmental delay. Many of the children appear to recover spontaneously, or perhaps learn tricks to circumvent their difficulties, by 9 or 10 years. The condition merits further, co-ordinated investigation.

Brain Injuries. Brain damage causing language disorder may result from birth traumas or defects of cellular metabolism in the perinatal period and, in later infancy and childhood, from cerebral inflammations or head injuries. It is often impossible to decide whether the gross language disorders which occur in the cerebral palsies are the result of damage to the auditory, motor, or interpretative functions of the brain, or to combinations of all these. Many of these children suffer from additional handicaps, such as deafness, eye defects, epilepsy, mental retardation, specific learning difficulties, disturbances of the body image and problems of behaviour. In other cases of confirmed or suspected brain injury motor disabilities may be slight or absent, and the presenting symptoms are learning difficulties, problems of behaviour, or

language disorders. All types of brain-injured children, however, have one characteristic in common. They tend to show, from day to day, a baffling inconsistency of response to testing procedures and to therapy, so that one is driven to the conclusion that essential connexions between the various brain mechanisms sometimes function and sometimes do not.

The whole question of speech therapy in cerebral palsy needs review. At present much time and energy are devoted to procedures which appear to be entirely empirical and almost exclusively concerned with improvement of articulation. Study of the available literature and discussions with many experienced speech therapists have brought me no nearer to understanding the fundamental neurological concepts which presumably underlie the practical procedures employed. Nor is it easy to assess results. The therapists' time might be more profitably spent in devising improved methods of communication for each individual child and in giving appropriate instruction to his parents and teachers. Detailed investigation and long-term follow-up of series of cases in association with paediatric neurologists and psychologists is urgently required. It is vitally important to discover whether or to what extent spoken language that is intelligible to the average listener can be produced by training, if it has not already begun to appear spontaneously by 7 years, and whether before or after this age alternative means of communication should be sought. It is true that the dysarthria of cerebral palsy usually improves in parallel with the general improvement in neuromuscular control. Squints also tend to improve, but the associated amblyopia may be irreversible.

Psychogenic Disorders. The disorders of spoken language which occur in the schizophrenias of childhood are only part of a grossly distorted development of intellect and personality. They vary from complete absence of speech to the use of neologisms, echolalia, or marked peculiarities of vocal intonation and stress. The one constant finding is an inability to use speech as a means of interpersonal communication. Language symbols seem to be lacking, although naming and parrot-like repetition may be retained. It is as if the child has the capacity to recognize and to repeat word forms but not to recall word meanings. He appears to be imprisoned in, or to have retreated to a small, insecure, and sometimes terrifying pre-linguistic, pre-body-image world of his own, from which he can only reach out in a fragmentary way to make contact with other people. His play is also solitary, meaningless, and non-progressive. I have not had the opportunity to observe groups of non-speaking psychotic children over a prolonged period of time, but in visits to hospitals and special units I have never seen them engage in the meaningful make-believe play normal nursery school children so richly invent, and which, in more primitive form, engrosses the attention of little mongols when they are given appropriate opportunities. The age when spoken language appears in psychotic children is of considerable prognostic significance. Kanner and Eisenberg (1955) have recently reported, in a long-term follow-up of 40 psychotic children, that of 19 who were not speaking by the age of 4½ years, only one subsequently did so. I cannot myself recollect ever seeing a child who had not begun to use spoken language by 6 years who later spontaneously developed it.

Conclusions

Given normal opportunity to learn, recognizable spoken words may be expected to appear between 14 and 20 months and by 2-2½ years the child is usually putting words together to make little sentences. The commonest causes of delay in the development of spoken language are deafness and mental backwardness. Full expert assessment of the hearing and the intelligence is, therefore, the first step in differential diagnosis. Regarding the rarer causes of delay it needs to be remembered that lesions of the central nervous system occurring in the first few years of life have been inflicted on plastic and rapidly growing tissues, and only time can tell whether the resulting damage is permanent, or capable of compensation, or open to recovery.

The first five or six years are therefore critical for diagnosis, treatment and training. However unpromising he may at first sight appear to be, the young child handicapped by a disorder of spoken language should be given the benefit of expert advice and supervision during these vitally important early years. Otherwise, lacking the means of communicating with his fellow beings, he may be condemned for the remainder of his life to emotional solitude and intellectual silence.

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THE NATURAL HISTORY OF INFANTILE SPASMS

BY

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The claim of Sorel to have improved the outlook for children with the syndrome of infantile spasms ('lightning spasms') and mental retardation by the use of corticotrophin (Sorel and Dusaucy-Bauloye, 1958; Sorel, 1959) has aroused widespread interest, and first reports have been enthusiastic (Low, 1958, 1959; Stamps, Gibbs, Rosenthal and Gibbs, 1959). Cortisone has also been said to be effective (Low, 1958; Dumermuth, 1959; Cox and Martin, 1959). It is now clear that these hormones produce some beneficial effect, but for a more precise assessment of their efficacy it is important to know the natural history of the disorder. In this paper we describe the clinical and electroencephalographic (E.E.G.) findings in 30 patients who have been followed up for periods varying from two to six years without the administration of hormones. They form a basis for comparison of the results of hormone treatment in 20 other patients (Bower and Jeavons, 1961).

Material

Thirty patients whose spasms began before the age of 12 months have been followed by clinical and E.E.G. examinations at approximately six-monthly intervals for a minimum of two years and a maximum of six years. Apart from the early examinations of a few of the older patients, which were made by the referring paediatricians, all clinical assessments were made by one of us (B.D.B.); and all E.E.G. records were interpreted by the other (P.M.J.). The clinical features of 20 of the patients have been described previously (Bower and Jeavons, 1959) and those of the remainder are similar. The numbers in each aetiological group are shown in Table 1. The symptomatic group consists mainly of children with a definite history suggesting prenatal or perinatal brain damage who had been mentally backward from birth. In addition, there is one infant who had measles encephalitis and was mentally retarded afterwards, and one child with tuberose sclerosis. Patients in the cryptogenic group, by contrast, had had an uneventful life with normal development until the onset of the spasms, and investigations gave no clue to the aetiology of their cerebral insult. In two patients developmental and birth history were paradoxical and they are therefore classified as 'doubtful'.

All patients were treated with one or more of the commonly used anticonvulsant drugs, for it is difficult to withhold them in such a distressing epileptic disorder even though there is general agreement that barbiturates, primidone, the diones, and drugs of the phenytoin group are ineffective. In our patients they had a negligible short-term effect and in all probability had no long-term effect, unless it was to suppress the major and focal fits which at times complicate infantile spasms.

Fourteen patients were at some time given a short course of a drug of the tetracycline group, but it is doubtful if this treatment produced any long-term benefit. Spasms were decreased in number or abolished in 11 of the 14 patients so treated, but in nine a relapse occurred shortly after the treatment was stopped; there was no clinical or E.E.G. evidence of more than temporary benefit in these nine patients, by comparison with the patients not given such treatment. In only two patients, therefore, could tetracyclines be given the credit for cure, and we think it more probable that administration of the drug coincided with natural cessation of the spasms.

There is therefore good reason to believe that the progress of all 30 children approaches that of the untreated case.

TABLE 1
AETIOLOGY

Aetiology	Nos.
Symptomatic	15
Prenatal or perinatal trauma or anoxia	13
Tuberose sclerosis	1
Measles encephalitis	1
Cryptogenic	13
Doubtful	2

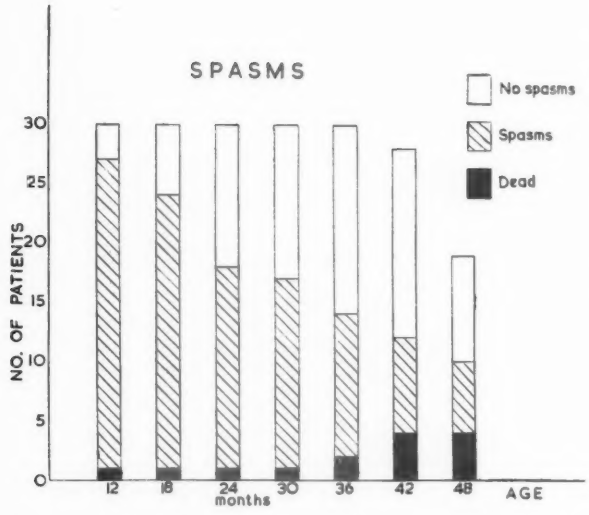

FIG. 1.—Numbers of patients with and without spasms (12-48 months).

Results

The Spasms. Fig. 1 shows the numbers of patients with and without spasms at each six-monthly period from the age of 12 months. All 30 were followed to the age of 36 months, and 28 to 42 months. At the age of 12 months, three patients had lost their spasms and one had died. There was a steady increase in the number without spasms as the patients grew older. At 36 months, over half (16) were free of them. At 42 months, four patients had died and only one-third of survivors still had spasms. Beyond that age numbers are smaller and conclusions cannot be drawn from them. It is interesting that one patient still has spasms at 6 years.

In addition to the tendency for this type of epilepsy to become less common with age, there was a tendency for the spasms to become less frequent and less severe in the individual patient. For instance, several of those shown in Fig. 1 as having spasms at 30 months, or later, merely had infrequent head nods. Five patients initially showed major or focal fits in addition to spasms, and three of these continued to have major fits over a long period. Five other patients developed major fits during the follow-up period.

It is of interest to compare the epilepsy in the symptomatic group with that in the cryptogenic group, and Table 2 shows the numbers of patients in each main group who at each age period still had spasms. It will be seen that there is little difference between the two groups. This suggests that age is a much more important factor than aetiology in determining the prognosis of the spasms once a patient develops them. Presumably some maturation factor is responsible for the inhibition of this type of epilepsy as the patient grows older and for the rarity of its onset after the age of 2 years.

There is one difference relating to the spasm in the two main groups. Six patients in the symptomatic group showed a lateralizing feature in the spasm; the head was flexed partly to one side, or the amplitude of limb movement was greater on one side than on the other. No patient in the cryptogenic group showed this feature.

TABLE 2

NUMBER OF PATIENTS IN EACH MAIN GROUP WITH SPASMS AT EACH AGE PERIOD

Age (yrs)	Symptomatic		Cryptogenic		Doubtful Aetiology
	No.	%	No.	%	No.
1	15 (15)	100	10 (12)	83	1 (2)
1½	12 (15)	80	10 (12)	83	1 (2)
2	9 (15)	60	8 (12)	67	0 (2)
2½	9 (15)	60	7 (12)	58	0 (2)
3	7 (14)	50	5 (12)	42	0 (2)
3½	5 (12)	42	3 (10)	33	0 (2)
4	5 (10)		1 (4)		0 (1)
5	1 (4)		0 (3)		
6	1 (1)		0 (3)		
7			0 (2)		

Bracketed figures indicate total surviving patients.

E.E.G. Findings. The scoring system, designed to separate the characteristics of hypsarrhythmia from those of non-hypsarrhythmic epilepsy, which was used in our previous study (Bower and Jeavons, 1959) was used again. Details are given in the Appendix. A hypsarrhythmic record scores 13-30 points. All records scoring 2-12 points were previously classified as 'non-hypsarrhythmic epilepsy'. However, we now label a record scoring 9-12 points as 'modified hypsarrhythmia', as it shows more organized epileptic activity than a truly hypsarrhythmic record and yet has some chaotic features. This category corresponds to hypsarrhythmia types 1 and 2 of Thiébaut, Sacrez, Röhmer and Isch-Treussard (1955). A record scoring 2-8 points shows centrencephalic or focal epilepsy, but is well organized. The total number of records taken and scored in the present study was 167.

Twenty-five patients had their first E.E.G. examination before the age of 12 months and our E.E.G. discussion is limited to these patients. All their first records were abnormal. The score was in the hypsarrhythmic range in 13, in the modified hypsarrhythmic range in four, and in the epileptic range in eight. Further E.E.G. examinations were carried out, as far as possible at six-monthly intervals; all 25 were followed to the 30-36 month age period,

and 23 to the 36-42 month period. Fig. 2 shows the number of patients with records in each E.E.G. category in each six-monthly age period.

It will be seen that there was an improvement in the E.E.G. up to the age of 42 months, just as there was an improvement in the epilepsy. In the 30-36 month period 10 records (over one-third) were normal, eight were epileptic, two showed modified hypsarrhythmia, and only three were frankly hypsarrhythmic. In the 36-42 month period the proportions were similar. There was a close correlation between individual clinical and E.E.G. improvement. Fifteen of the 25 lost their spasms during follow-up; 10 of these 15 had a normal E.E.G. at the next and all subsequent examinations. The remaining five showed (non-hypsarrhythmic) epileptic E.E.G. abnormalities and three of these patients had occasional major fits after the spasms had ceased. The E.E.G.s of the eight whose spasms continued were abnormal (five showed hypsarrhythmia or modified hypsarrhythmia and three were epileptic).

Comparing the scores in the symptomatic and cryptogenic groups, we found that on average the scores in the former group were higher than those in the latter, both initially and throughout the subsequent six-monthly periods. Moreover, the cryptogenic group tended to produce normal records earlier.

Since six children in the symptomatic group showed a focal element in their spasms, one might expect a higher incidence of lateralized focal E.E.G. abnormality in this group. Four of these six children showed such abnormalities. However, 12 of the 25 children showed focal E.E.G. abnormalities at some time, and five of them belonged to the cryptogenic group. The foci often changed to the opposite side in subsequent E.E.G. records and, since disappearance, reappearance and 'wandering' of foci are quite common features of the E.E.G.s of epileptic children in general, their presence in our patients is probably not important. They do not necessarily indicate localized cerebral change, though they may be significant in association with clinical lateralization.

Mentality. Unfortunately there was no corresponding general improvement in mentality (Fig. 3). The mental level was graded in each case as gross retardation (corresponding to amentia), moderate retardation or normal. The abilities of two patients at the age of 12 months illustrate the two categories of mental retardation:

GROSS RETARDATION. A. was unable to sit or hold his head up. He could not grasp an object even when put into his hand. He could not recognize his mother and appeared blind. There was no response to voice, and he did not vocalize spontaneously. Movements were aimless, generalized, and incoordinate.

MODERATE RETARDATION. J. could sit and stand unaided, and retained an object if placed in the hand. However, he was not interested in his surroundings; he only fixed with his eyes for a few seconds and showed

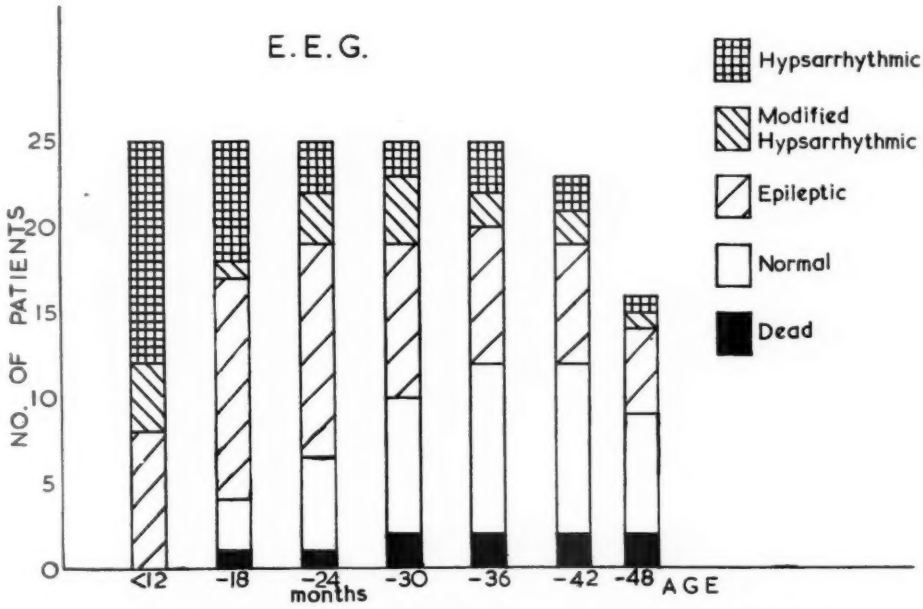

FIG. 2.—Number of patients with E.E.G.s in various categories (<12-48 months).

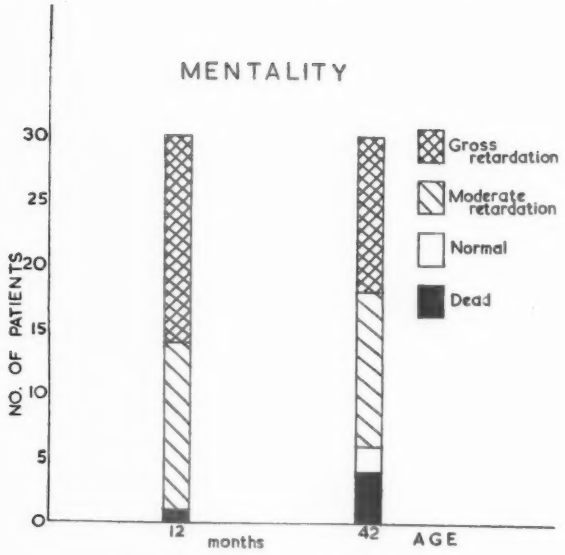

FIG. 3.—Mentality at 12 and 42 months.

little emotional response to social overture. He did not laugh, and smiled only briefly and occasionally. Vocalization consisted of only two or three sounds. He showed the relatively slight motor retardation commented upon by Illingworth (1955).

At 12 months, 16 patients were grossly retarded and 13 were moderately retarded; one had died. Twenty-eight of the 30 patients have now reached the age of 42 months; 11 are grossly retarded, 12 moderately retarded, one patient is mentally normal, and four patients have died. The remaining two patients are 36 months old and in view of their past history it is most unlikely that their state will change in the next six months; one is grossly retarded and one is mentally normal. In Fig. 3 they are therefore treated as if they were 42 months old. The two patients who have regained normal mentality were both in the cryptogenic group, had a low E.E.G. score on their first record (4 and 5), and their second and subsequent E.E.G.s were normal. They lost their spasms early (at 7 and 20 months). One received tetracycline.

Comparing the two groups, both at 12 months and subsequently, there is a great preponderance of grossly retarded children in the symptomatic group (Table 3). Even though patients in the cryptogenic group may be grossly retarded shortly after the onset, some pass into the moderately retarded category within a few months. Only two children in the cryptogenic group were grossly retarded at 12 months and both were only moderately retarded at 42 months. The improvement in this group was maintained after this age in the older patients reviewed. For instance, three children in the cryptogenic group are now over 5 years of age. All three are pleasant children, relatively obedient, able to communicate with short sentences, and have no neurological deficit. They are probably all mildly retarded, but two attend a normal school. By contrast, the four in the symptomatic group who are over 5 years old are grossly retarded and obviously ineducable.

Mortality. Four patients died, one at 5 months and the others at between $2\frac{1}{2}$ and $3\frac{1}{2}$ years. Two were in the symptomatic group and two in the cryptogenic group.

Discussion

Apart from the reports of Gibbs, Fleming and Gibbs (1954) and Livingston, Eisner and Pauli (1958) there is little detailed information in the literature about the prognosis of patients with infantile spasms. Most authors agree that in general the spasms tend to diminish with age, the E.E.G. pattern becomes more organized and may become normal, but the mental retardation usually persists unaltered. Of our surviving patients 57% were free of spasms at $3\frac{1}{2}$ years and this compares with 43% at 3-4 years, reported by Gibbs *et al.* (1954). Livingston *et al.* (1958) report that less than 1% of their patients with minor motor epilepsy (equivalent to infantile spasms) still had spasms after 5 years of age. Only eight

TABLE 3
MENTAL ASSESSMENTS AT 12 AND 42 MONTHS IN THE TWO MAIN GROUPS

Aetiology	At 12 Months			At 42 Months			
	Retardation			Retardation			
	Gross	Moderate	Dead	Gross	Moderate	Normal	Dead
Cryptogenic group ..	2	10	1	0	9	2*	2
Symptomatic group ..	13	2	0	10*	3	0	2
Doubtful aetiology ..	1	1	0	2	0	0	0
Total	16	13	1	12	12	2	4

* One patient only 36 months old.

of our patients have reached this age so we cannot compare our figures with theirs.

The E.E.G.s of our patients during follow-up appear to be less abnormal than those of Gibbs *et al.* (1954). Of our patients, at 3-3½ years, 19% had typical or modified hypsarrhythmia, compared with 53% of their patients at 3-4 years; and at these ages 47% of our patients and 20% of theirs had normal records.

Both Gibbs *et al.* and Livingston *et al.* show that it is rare for these patients to survive this form of epilepsy with normal intelligence. The latters' figure for mental normality is 1·8%, and ours (in a much smaller series than theirs) is 7·7%. Burnett, Gibbs and Gibbs (1958) show that the prognosis is much better if the initial E.E.G. is normal. It is of interest that the two patients in our series who became mentally normal each had only one abnormal E.E.G. and this had a low score. Of our patients, 44% were grossly retarded and, although details of the severity of the mental defect are not given in the above publications, it is clear that gross retardation was fairly common, for in each series 23% were institutionalized.

The mortality rate in our series (13% of 30 patients) is similar to that of Gibbs *et al.* (11% of 103 patients) up to the age of 3 years. Livingston *et al.*, however, found that by 6 years only 3·7% of 622 patients had died.

Our patients show definite prognostic differences in the symptomatic and cryptogenic groups, and this is not commented upon by previous authors. The patients in the symptomatic group were initially more severely retarded, some had spastic diplegia or hemiplegia, and microcephaly was common, in contrast to the cryptogenic group. It is therefore not surprising that, in view of this clear evidence of more severe brain damage in the symptomatic group, they should show no mental improvement during follow-up, whereas there is a slight tendency for the cryptogenic group to improve. Although the numbers followed to the age of 6 are small, the clear-cut difference in mental level in the two groups at that age confirms this prognostic difference. By contrast, the two groups behaved similarly with regard to the rate of disappearance of spasms, although there is perhaps a tendency to earlier disappearance in the cryptogenic group after 2 years. The E.E.G.s are more chaotic in the symptomatic group at all ages.

Summary

Thirty infants with the syndrome of infantile spasms and mental retardation occurring before the age of 1 year have been followed by clinical and E.E.G. examinations for periods of two to six years. None were treated with corticotrophin or steroids.

There was a steady reduction in the number still having spasms and at 3 years over half the patients were free of them. Focal or major fits occurred in one-third of the total and did not show the same tendency to disappear with age.

The E.E.G.s became more organized and at 3-3½ years more than one-third were normal. Hypsarrhythmia was rare by this age but was found even at 6 years.

Mental improvement was much rarer and only two patients became mentally normal.

The mortality rate was 13% by 3½ years.

There was little difference between the symptomatic and cryptogenic groups with regard to the rate of disappearance of spasms and E.E.G. improvement. Mental retardation, however, was less severe in the cryptogenic group even at 1 year and this group showed a slight but definite general improvement later, whereas none occurred in the symptomatic group.

Our thanks are due to the consultant physicians of the Children's Hospital, Birmingham, and the consultant paediatricians of the Birmingham Region for allowing us to examine their patients; to Professor D. V. Hubble for encouragement and advice; and to Mrs. Trilloe, Miss D. J. Campbell, Miss M. E. Dyas and Miss A. E. Hill for their skilful performance of E.E.G. examinations on these difficult patients.

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APPENDIX

It is notoriously difficult to analyse and describe the records of young children and therefore a scoring system (based on examination of 180 records) was devised to enable more precise comparison to be made between different cases and to assess change in the same case. The scoring system is designed to give maximum marks to utterly chaotic tracings and minimum marks to highly organized epileptic records. The records are divided into nine grades:

		Score
Grade 1:	Complete chaos, with total asynchrony, no organized discharges and no normal background activity	12 points
Grade 2:	Chaos, with some discernible synchronous bursts. The bursts were of chaotic make up, and the episodic nature could only be seen by reducing the gain	8 points
Grade 3:	Mainly chaotic, but with more bilaterally synchronous activity than Grade 2	6 points
Grade 4:	Bursts of chaotic make-up, some bilaterally synchronous discharges and a little normal background activity	4 points
Grade 5:	Discharges mainly bilaterally synchronous, but some showing a chaotic make-up. Some normal activity	3 points
Grade 6:	Bilaterally synchronous epileptic discharges (centrencephalic). No chaos. Normal background activity	1 point
Grade 7:	Focal epileptic discharges. No chaos. Normal background activity	1 point
Grade 8:	Non-specific abnormality	1 point
Grade 9:	Normal	Nil

The grading is made on the overall appearance of the record, and it is therefore not possible to give illustrations of the different grades.

In addition to being given a grade score the different components of hypsarrhythmia are scored as follows:

(*a*) Amplitude. High voltage is probably the most common finding, at times being over 900 microvolts.
Voltage normal or up to twice normal for age: 1 point.
Voltage two to four times normal for age: 2 points.
Voltage over five times normal for age: 4 points.

(*b*) Bursts of very chaotic make-up, containing delta waves from 0·75 c/s to 3 c/s, with spikes of varying site and amplitude: score 2 points.

(*c*) Bursts of slow or rapid spikes appearing simultaneously in all regions: score 2 points.

(*d*) Focal spikes: score 1 point each for left, right, or posterior.

(*e*) Completely random spikes: score 4 points

(*f*) Completely random delta: score 2 points.

Normal background activity scores minus 1 point.

Using the above method a completely hypsarrhythmic record scores 13-30 points; modified hypsarrhythmia scores 9-12 points; an epileptic record of centrencephalic type and a focal epileptic record scores 2-8; a normal or non-specific record scores 0 or 1 point respectively.

THE EFFECT OF CORTICOTROPHIN AND PREDNISOLONE ON INFANTILE SPASMS WITH MENTAL RETARDATION

BY

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The immediate effects of the use of corticotrophin or cortisone in patients with infantile spasms may be dramatic (Sorel and Dusaucy-Bauloye, 1958; Low, 1958; Sorel, 1959), but the more permanent results are less easily assessed. There is still no confirmation of Sorel's claims that corticotrophin can produce prolonged benefit, in particular mental improvement, for long-term improvement can occur without such treatment. This paper reports an attempt to assess the immediate and later results of treatment with corticotrophin and prednisolone by comparison with the findings in patients not treated with hormones (Jeavons and Bower, 1961).

Material and Method

Twenty-three children with infantile spasms have been treated with corticotrophin or prednisolone or both. Of these, 21 were treated personally. E.E.G. examinations of the remaining two, who were treated by Drs. J. S. Oldham and H. McC. Giles, were performed in our departments and their records have been assessed in the same way as those of our patients. All patients had an abnormal E.E.G. before treatment and all were mentally retarded.

Twelve patients are classified as belonging to the cryptogenic group. Mental development was normal until the onset of the epilepsy and in 11 there was no clue to the cause of the cerebral damage. In the twelfth patient, spasms started three days after his first injection of poliomyelitis vaccine, but since the relevance of this event to the disorder is uncertain, he is included in this group.

The other 11 patients are classified in the symptomatic group. Mental retardation was present from birth and there was evidence suggesting a definite cause for cerebral damage (Table 1). In 10 cases the cause was a perinatal factor or combination of factors, while in one it was cerebral agenesis with absence of the corpus callosum. In one patient spasms had already ceased before treatment but, as he was mentally retarded and his E.E.G. was still abnormal, treatment was given and his case is included.

All patients were treated in hospital for at least four weeks. If E.E.G. improvement was still occurring at the end of that time, treatment was continued until a steady state was reached. Eight patients were given a second month's treatment because relapse followed the first course or because the first course was ineffective. In one instance a third course was given, as an outpatient. With the exception of the first two cases treated and one very young patient, the daily dose of corticotrophin was 20-30 units, according to age. The drug

TABLE 1
SYMPTOMATIC GROUP
FACTORS LEADING TO DIAGNOSIS OF PRENATAL OR PERINATAL BRAIN DAMAGE

Case	History	Micro-cephaly	Other Evidence
S.1	Pitocin drip, precipitate labour	Yes	—
S.2	—	No	Cerebral agenesis with absence of corpus callosum (pneumoencephalography)
S.3	Precipitate labour; spasms from second day	Yes	Cerebral diplegia
S.4	Premature (birth weight 3 lb. 5 oz.)	Yes	—
S.5	Caesarean section for foetal distress; neonatal cyanotic attacks	Yes	—
S.6	Antepartum haemorrhage, foetal distress	Yes	Symmetrical ventricular dilatation (pneumoencephalography)
S.7	Prolonged labour; neonatal cyanosis	No	Hemiparesis
S.8	Premature; neonatal 'jumps' and cyanotic attacks; did not cry for three weeks	Yes	—
S.9	Neonatal hypotonia; would not cry or suck for six weeks	No	—
S.10	Drowsiness and failure to suck in neonatal period	Yes	—
S.11	Forceps delivery; head bruised	No	Mild hemiparesis

was given 12 hourly by injection, in the gel form. Prednisolone was given six hourly by the oral route, the daily dose being approximately 1 mg. per lb. body weight. In a few instances the dose was altered later in the course, and at the end of treatment reduction was made gradually. Details of treatment are shown in Tables 2 and 3.

Progress was judged in three parameters. The spasms were charted by the nursing staff. Although some may have occurred unnoticed, these were probably few, for there is a good correlation between the presence or absence of spasms as charted and the E.E.G. state. Moreover, spasms usually occur in a series lasting several minutes and the initial cry often draws the attention of the nurse to the event. Nevertheless, we shall consider them as 'present', 'fewer' or 'absent', rather than by numbers recorded.

E.E.Gs were recorded twice weekly during hospital stay and as often as was convenient after discharge. At the beginning of the study they were scored in a random order by one of us (P.M.J.) with no knowledge of the patient's treatment at the time. Later, with increased confidence in the method, records were scored as treatment proceeded, in order to help in deciding the length of treatment necessary in each case. The scoring system is described elsewhere (Jeavons and Bower, 1961). In all, 481 E.E.G. records were taken. Mental assessment was performed by Griffiths testing before treatment, within three weeks after stopping treatment, and at intervals during the follow-up period.

Results: The Cryptogenic Group (12 cases)

The Immediate Results. These are shown in detail in Table 2.

SPASMS. These ceased in all patients during the first course of treatment, whichever drug was used. In five this occurred during the first week, but in two patients it did not occur until more than five weeks of treatment had been given. One patient (C. 12) who had major fits in addition to spasms, continued with intermittent major fits during treatment despite control of spasms and, on withdrawal, developed status epilepticus.

Relapse occurred in eight patients within three weeks of stopping treatment, usually within the first week.

E.E.G. There was also a definite E.E.G. improvement in all patients during the first course of treatment. In 11 the score fell and reached 4 or less (i.e. non-hypsarrhythmic). In the twelfth (C. 5) the initial record was highly organized and scored only 2. Her records were therefore assessed by counting the percentage of the total recording time which was occupied by epileptic activity. This fell from 65% before treatment to 10% during treatment.

TABLE 2

CRYPTOGENIC GROUP: TREATMENT AND IMMEDIATE RESULTS

Case	Age at Start of Treatment (mths)	Duration of Spasms Before Treatment (mths)	Treatment			Immediate Results						
						Spasms		E.E.G.			D.Q.	
			Drugs	Duration (wks)	Daily Dose (C: i.u. P: mg.)	On Treatment	After Treatment	Pre-treatment Score	Lowest Score During Treatment	Post-treatment Score	Before Treatment	After Treatment
C.1	6	¾	C	7	25→30 (reduction after four wks)	O	O	22	0	0	Low	Low*
C.2	7	2	(1) P	7	20	O	R	10	3	3	46	34
			(2) P	4	15	F	R	3	3	3	34	36
C.3	6	2	P	6	20	O	R	17	1	2	53	45
C.4	8	3	(1) C	5	5	O	R	18	4	10	23	—
			(2) C	4	20	O	R	16	1	5	—	20
C.5	13	3	P	4	30	O	R	2	2	2	40+	43
C.6	13	5	(1) C	4	25→30	O	R	4	0	2	60	64
			(2) P	16	20→15 →10	O	O	2	0	0	64	80
C.7	13	7	P	5	25	O	R	12	0	3	22	22
C.8	13	8	C	5	10	O	O	13	2	2	55	46
C.9	25	16	C	10	20→30	O	O	26	0	0	Low	Low
C.10	35	17	C	4	20	O	O	8	0	0	50	45
C.11	42	25	(1) C	4	20	O	R	11	4	10		
			(2) C	4	25	O	R	10	2	6	Low	Low
			(3) P	34	20	F	R	6	3	3		
C.12	42	36	(1) C	4	30	O	R	12	2	11	8	9
			(2) P	20	20→15	F	R	16	12	14	9	14

C = Corticotrophin O = No spasms P = Prednisolone F = Fewer spasms than before treatment R = Relapse after treatment

* This child subsequently reached 83.

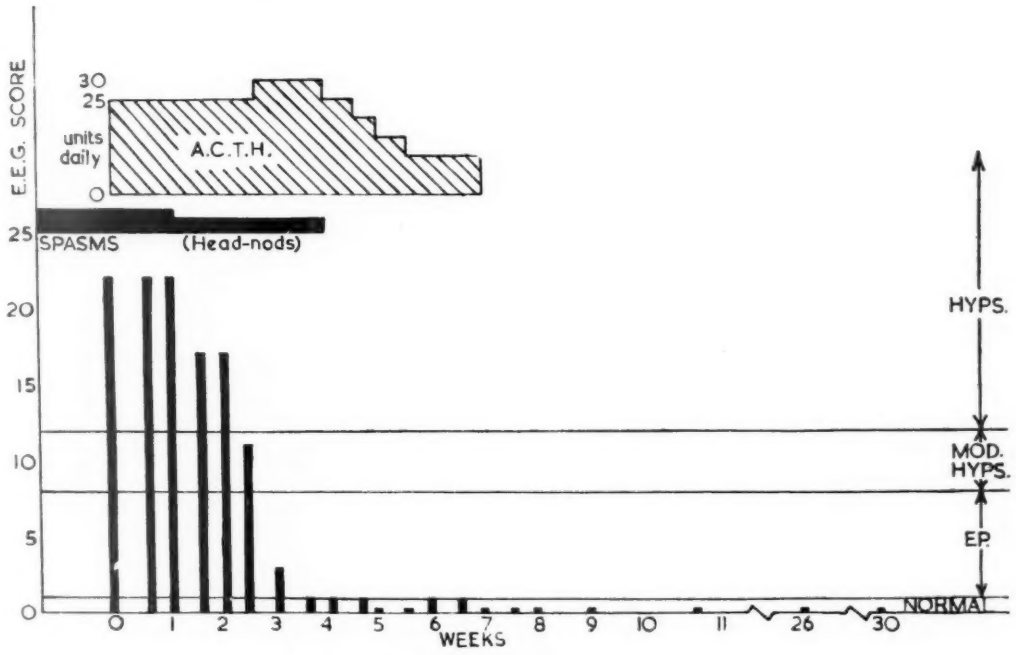

FIG. 1.—Response of spasms and E.E.G. to corticotrophin (patient C.1).

A record showing no epileptic activity (score 0 or 1) was obtained in six patients, and three of these showed completely normal records during the remainder of the course.

In only one patient did all epileptic abnormality disappear within the first week. In four the score was 3 or less before the end of the second week. There was no constant relationship between cessation of spasms and the E.E.G. score at that time. Sometimes spasms ceased before marked E.E.G. improvement occurred but at other times E.E.G. improvement preceded cessation of the spasms. However, the two events usually occurred within one week of each other. The time taken to achieve a non-epileptic record varied from seven to 64 days, and the speed of response was unrelated to the daily dose or the drug used. Fig. 1 shows a satisfactory response to corticotrophin, and Fig. 2 a similar but less complete response to prednisolone in another patient.

The E.E.G. improvement took the following form: First there was a gradual reduction in chaos, then a more normal activity emerged, with episodic bursts of chaotic wave-and-spike activity; then the epileptic discharges became more organized and tended to be bilateral, and slow wave-and-spike activity at 2 c./sec. appeared. At this point there was a tendency for unilateral abnormality to appear and some records showed focal spiking, most commonly in the temporal regions. Many records continued to show bilaterally synchronous epileptic discharges, and only a few became normal.

In seven patients there was a deterioration after treatment was stopped, but in one of these (C. 6) there was no deterioration after a second course. (This course was unusually long but the daily dose was low for much of the time.)

MENTALITY. There was no immediate dramatic mental improvement. In eight patients comparison of development quotients (D.Q.s), estimated before and within three weeks after treatment, showed no significant improvement. A ninth patient showed no improvement between an initial score and the score obtained after a second course of treatment (no test was performed between the first and second courses). In the remaining three, where only clinical assessment was used, again no improvement was observed. In several instances there was an apparent improvement; the child became livelier, sat up for the first time, or showed some other ability which was previously absent. However, full developmental testing showed no all-round improvement and the score remained at approximately the same figure. Probably the apparent advancement merely represented steroid euphoria. In four patients the score actually fell.

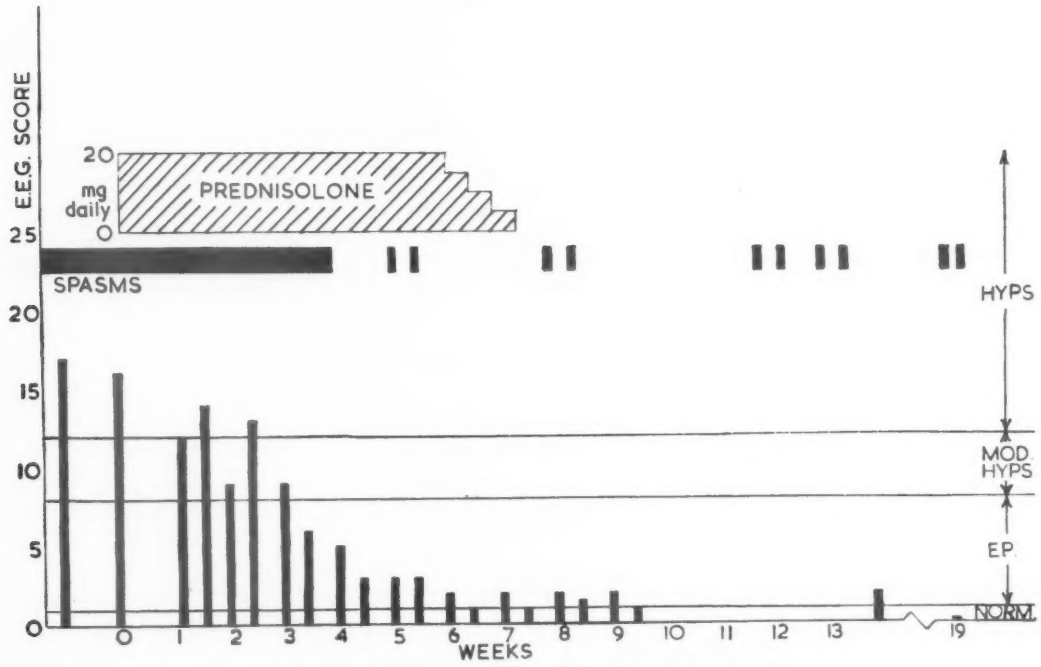

FIG. 2.—Response of spasms and E.E.G. to prednisolone (patient C.3).

Later Results. Five of the patients who relapsed after the first course were given another course of corticotrophin or prednisolone, and one received a third. In only one patient (C.6) was another course more successful than the first in preventing a recurrence. This child also showed a significant mental improvement, in contrast to the others. Her second course was prolonged, lasting 16 weeks.

The period of follow-up varies from three to 14 months from the start of treatment, the average being eight months. During follow-up two more patients became free of spasms (C.5 and 7), making a total of seven who have lost their spasms.

Mental progress was assessed by Griffiths testing in 10 cases (Fig. 3). In seven there was no significant improvement (an increase of more than 10% over the pre-treatment score). Two of the remaining three patients (C.1 and 6) have achieved a D.Q. of 80. Unfortunately one of them (C.1) was not assessed by Griffiths testing before treatment but he was obviously retarded and, from questioning, it appeared that his D.Q. was probably between 50 and 60. The initial score of the other (C.6) was 60 and it rose to 80 after the second course of treatment. Four months later there had been no further rise. Both these patients were free of spasms and their E.E.G.s remained normal after treatment. The third patient (C.8) has shown an advance of 11 points, to reach 66 12 months after starting treatment. He also has had no spasms after treatment but his E.E.G. still shows a mild epileptic abnormality (score 2). The two patients not assessed by Griffiths testing, judged clinically, have shown no mental improvement.

In summary, the immediate results were dramatic as regards cessation of spasms and E.E.G. improvement but, after cessation of treatment, spasms recurred in eight patients and the E.E.G. deteriorated in seven. Only one of these eight patients did not relapse after a second course of treatment. After an average follow-up period of eight months, seven patients are free from spasms. The influence of treatment upon mental retardation has been disappointing. Only three patients have achieved an increase in D.Q. of more than 10% during the follow-up period and in no patient was this improvement immediate.

Results: The Symptomatic Group (11 patients)

The Immediate Results. These are shown in detail in Table 3.

SPASMS. These ceased during the first course of treatment in only six patients, but in three others they became fewer. Only one patient was uninfluenced by treatment. The remaining patient (S.9) had already lost his spasms before treatment

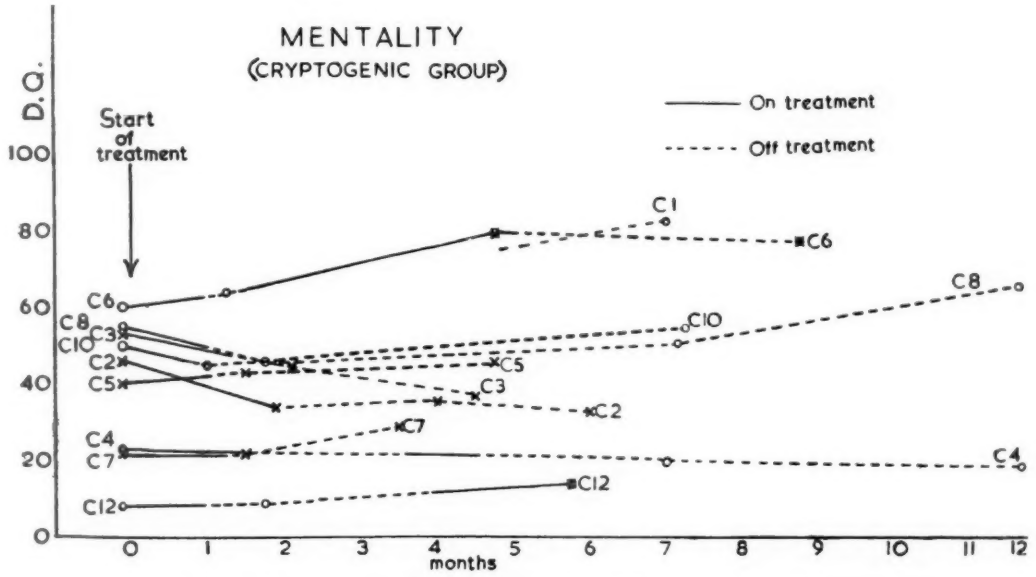

FIG. 3.—Mentality (D.Q.) during follow-up (10 patients in the cryptogenic group). O = treated with corticotrophin; X = treated with prednisolone.

was started. Relapse occurred in seven patients, one maintained relative improvement, and only one patient achieved complete freedom from spasms after the course. Recurrence occurred within one week of stopping treatment in three patients and within four weeks in the other four.

E.E.G. There was an improvement during treatment in 10 of the 11 patients. Frank hypsarrhythmia was abolished, although the lowest score of one patient was in the 'modified hypsarrhythmia' range. A non-epileptic record (score 0 or 1) was achieved in three patients. Improvement took the same form as it did in the cryptogenic group.

Deterioration after treatment was stopped occurred in 10 patients.

MENTALITY. There was no significant improvement in any patient. This is not unexpected, in view of the fact that these patients had suffered

TABLE 3

SYMPTOMATIC GROUP: TREATMENT AND IMMEDIATE RESULTS

Case	Age at Start of Treatment (mths)	Duration of Spasms Before Treatment (mths)	Treatment			Immediate Results						
						Spasms		E.E.G.			D.Q.	
			Drugs	Duration (wks)	Daily Dose (C: i.u. P: mg.)	On Treatment	After Treatment	Pre-treatment Score	Lowest Score During Treatment	Post-treatment Score	Before Treatment	After Treatment
S 1	5	4 days	C	8	25→30	O	R	7	0	2	35	33
S 2	2½	1½	(1) P	3	12·5	U	U	6	6	9	Low	Low
			(2) C	4	25	F	R	13	3	6		
S 3	2	2	(1) C	2*	5	F	F	14	2	12	Low	Low
			(2) P	6	7·5→10	O	R	12	3	7		
S 4	9	2	C	6	15→20	F	R	15	9	14	35	28
S 5	6	3	(1) C	4	25	O	R	16	5	7	33	31
			(2) P	4	20	F	R	15	4	17	25	Lower
S 6	12	5	C	4	25	O	R	9	2	10	12	2
S 7	8	6	C	10	10→20	O	O	21	1	1	32	21
S 8	16	10	P	4	20	F	R	17	6	14	4	6
S 9	13	—	P	4	20	—	—	6	0	2	14	20
S.	21	15	P	4	20	O	R	12	2	10	2	2
S.	50	41	P	4	40	O	R	15	4	10	Low	Low

C = Corticotrophin O = No spasms P = Prednisolone F = Fewer spasms than before treatment R = Relapse U = Unchanged

* Developed cardiac failure.

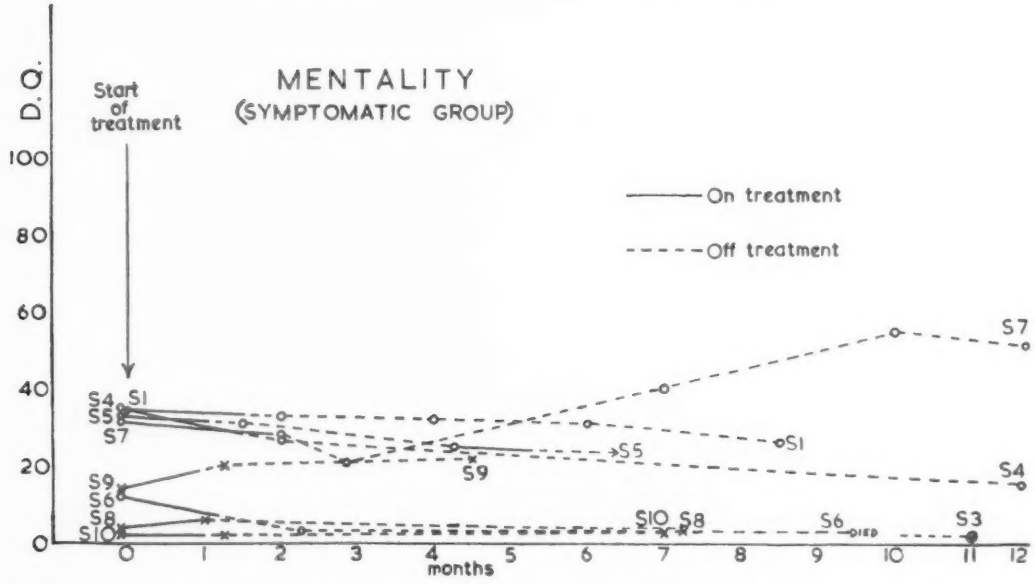

FIG. 4.—Mentality (D.Q.) during follow-up (nine patients in the symptomatic group). O = treated with corticotrophin; X = treated with prednisolone.

brain damage at or before birth; seven were microcephalic and marked cerebral atrophy was demonstrable in another.

Later Results. Three patients were given a second course of treatment, using the alternative drug. In all three cases, although there was a response, a clinical and E.E.G. relapse occurred after the second course similar to that after the first (Fig. 5).

The period of follow-up (10 patients) varied from four months to 12 months from the start of treatment, the average again being eight months. Spasms stopped in two patients during this period, making a total of four free from spasms. The E.E.G. showed an increase in score after treatment and, although in some patients there has been a reduction of score since then, only one patient (S.7) has had a non-epileptic record since treatment. One patient (S.6) had been unable to attend for E.E.G. examination since six weeks after treatment was stopped but his E.E.G. score then was as high as it had ever been. He has since died.

Mental progress was assessed by Griffiths testing in nine patients (Fig. 4). Only one patient (S.7) has shown an increase in D.Q. of more than 10%. He has only reached 52% but his performance is handicapped by a mild hemiparesis. He is the only patient whose epileptic and E.E.G. improvement was sustained after treatment. His treatment lasted longer than that of any other patient in the symptomatic group, although in the first months the daily dose was lower than the usual dose given. The remaining two patients, judged clinically, have shown no mental advance. One is a spastic ament. The other is aged 4½ years with a mental age of about 9 months.

In summary, the immediate results were qualitatively similar to, but not as dramatic as, those of the cryptogenic group. Spasms ceased during treatment in six patients and became fewer in three, and the E.E.G. improved in every patient but one. With one exception, relapse occurred in all patients after treatment, and relapse followed a second course given to three patients. After an average follow-up period of eight months, four patients are free from spasms. As expected, there was no overall mental improvement. One patient, however, has shown an increase in D.Q. of more than 10% during follow-up but he is still definitely retarded.

Discussion

Immediate Effects. From our results we agree with Sorel and Dusaucy-Bauloye (1958), Sorel (1959), Low (1958, 1959), Gastaut, Saltiel, Raybaud, Pitot and Meynadier (1959), Dumermuth (1959) and Stamps, Gibbs, Rosenthal and Gibbs (1959) that corticotrophin abolishes or greatly reduces the frequency of infantile spasms and improves the

E.E.G., even to the point of normality. Cortisone has been credited with a similar effect (Low, 1958; Cox and Martin, 1959; and Dumermuth, 1959). Since prednisolone has a smaller salt-retaining effect than cortisone or corticotrophin, we decided to use it to treat some patients in order to compare its effects with those of corticotrophin, for if it was as successful as the other two drugs, it would have obvious advantages. Our results show that it has an effect similar to corticotrophin. A detailed comparison is made below. Disregarding for the moment any differences in the efficacy of the two drugs and considering the overall effect of hormone treatment, we see that spasms ceased in 81% of patients during treatment. The E.E.G. improved in 95%, becoming non-epileptic in 39%. The pattern of improvement was similar to that of the untreated series (Jeavons and Bower, 1961), but the improvement occurred in a matter of three to four weeks in the treated cases whereas it took months or years in the untreated cases.

Relapse after Treatment. Most of the above authors describe cases who relapse after treatment, but regard them as infrequent. By contrast, such cases form the majority in our series. Fifteen of our 21 patients whose spasms diminished or stopped during treatment relapsed within three weeks after treatment, whereas Sorel (1959) found a relapse in only two out of 10 patients treated with corticotrophin and Stamps *et al.* (1959) found a relapse in nine out of 36 who responded.

Since the tendency to relapse is greater in the symptomatic than in the cryptogenic group, one explanation of this difference might be that the above authors' series contained a higher proportion of cryptogenic cases than ours. Unfortunately, precise aetiological classification of their patients is difficult. However, the relapse rate is higher in our series, even if we only consider the cryptogenic group (eight out of 12). Another possibility is that our patients were treated at a later stage of the disease. Sorel (1959), Gastaut *et al.* (1959) and Low (1958, 1959) all consider that the earlier treatment is given, the better will be the results. Three of Sorel's patients started treatment within one month of onset, and two of ours did so. The average period between onset and treatment was eight months in Sorel's cases, and 10 months in ours. (Information is insufficient to allow comparison of our cases with those of the other authors.) It seems unlikely that the difference in results can be explained on the basis of such slight differences in timing of treatment. Nor does an age factor account for it, for the average ages of Sorel's patients and ours are similar. We usually gave

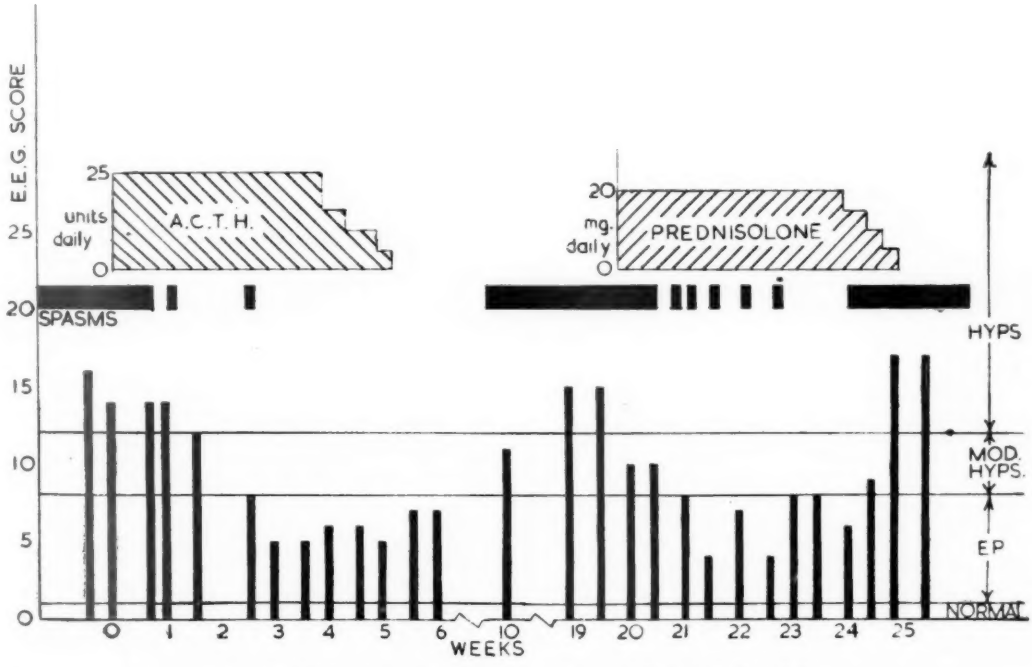

FIG. 5.—Response to corticotrophin and to prednisolone (patient S.5).

a larger dose of corticotrophin than Sorel did and treatment was at least twice as long, so that our treatment was more than adequate by his standards. A possible explanation of the overall relapse rate is that prednisolone is less efficient in preventing a relapse than corticotrophin, which was the only drug used by Sorel. The two drugs are compared below.

Later Effects. Although our follow-up is as yet short (average eight months) it is interesting to try to assess whether treatment has long-term effects, or whether later improvement in the epilepsy is entirely due to the natural tendency to improve with age. In order to eliminate the immediate effect of treatment, we shall only consider patients who have been off treatment for more than three months. At the age of 12 months there were five such patients. Three of these had no spasms. At 18 months there were six such patients, and four had no spasms. In our series of untreated patients only three out of 29 had no spasms at 12 months and only six out of 29 at 18 months. Although numbers are small, this comparison suggests that the treatment had a prolonged beneficial effect on the epilepsy, and this suggestion is borne out by a consideration of E.E.G. scores. At 12 months, three of the five treated patients had non-epileptic records, by comparison with none of the 25 untreated patients, and at 18 months, two of the six treated patients had non-epileptic records, by comparison with three out of 24 in the untreated group.

Comparison of Corticotrophin with Prednisolone. There are obvious difficulties in comparing two drugs with a similar effect when patients differ in age, and their epilepsy differs in severity, aetiology and duration. However, such a comparison is justified in our series because the patients in each treatment group have the same average age (16 months), similar average durations of symptoms (nine and 10 months) and are equally distributed between the cryptogenic and symptomatic groups.

Both drugs were equally effective in controlling spasms during treatment. Considering first courses only, 12 out of 14 patients treated with corticotrophin lost their spasms, compared with six out of eight given prednisolone. However, there was a much higher relapse rate after prednisolone than after corticotrophin. All six patients whose spasms stopped during prednisolone treatment relapsed afterwards, whereas only seven of the 12 who responded to corticotrophin did so. Corticotrophin was also more effective in producing a normal E.E.G. Seven out of 14 treated with corticotrophin achieved a non-epileptic record, compared with two out of eight treated with prednisolone. The main difference was in the cryptogenic group. Fig. 5 illustrates the similar response to each drug shown by a patient in the symptomatic group.

We conclude, therefore, that corticotrophin is in general a little more effective than prednisolone. However, this conclusion refers only to the doses used by us. It is possible that a higher dose of prednisolone than 1 mg. per lb. body weight per day would have achieved better results, although this is the usual dose employed in paediatric practice to obtain maximal effects. We have some evidence that the amount of endogenous adrenal steroid produced by patients given corticotrophin differed little from the amount of exogenous steroid given to prednisolone-treated patients. The daily urinary output of 17-hydroxycorticosteroids was estimated weekly in nine of the corticotrophin-treated patients. The maximal output was found to be between 10 and 20 times the basal output. This is evidence of adequate adrenal response, approximating to the dose of prednisolone given to the prednisolone-treated group. It is not possible to compare more accurately the quantities of steroids available from these exogenous and endogenous sources.

Mentality. Mental retardation is the most disabling feature of the clinical syndrome and the claim of Sorel (1959) that it can be abolished by corticotrophin is of paramount importance. Assessment of mental improvement is, of course, often difficult in these very young patients and all publications are inadequate in the data given. Except where a child is said to be normal, it is difficult to judge how much improvement has occurred. It was for this reason that we decided to attempt more precise assessment of mental improvement by using Griffiths testing.

It will be seen (Figs. 3 and 4) that initial scores are, in general, lower in the symptomatic group than in the cryptogenic group. Indeed, there are four in the symptomatic group who score less than 20 compared with one such patient in the cryptogenic group. This confirms our clinical assessment that patients in the symptomatic group tend to be more severely retarded (Jeavons and Bower, 1961).

No patient showed a significant increase in score immediately after the first course of treatment. We cannot therefore confirm the statements of Sorel and Dusaucy-Bauloye (1958) and Gastaut *et al.* (1959) that rapid mental improvement occurs in some patients. In several instances the scores actually fell. Occasionally a child appeared more alert or showed some new ability, but testing

after the course showed no general advancement in D.Q.

It would perhaps be surprising if there were a great advance in mental level within a few weeks of cessation of spasms, and it is of more relevance to know whether there is mental advancement over a long period, particularly when the child has been free from spasms and the E.E.G. has been normal for some time. We cannot yet answer this fully, but it is already clear that, in a minority of patients, whose spasms are arrested, a significant increase in development quotient has occurred. The D.Q.s of four patients have increased by more than 10 over the pre-treatment figure. Only two, however, have reached 80 or over, and can therefore be included in the normal range (Griffiths, 1954). It is the opinion of Sorel and Dusaucy-Bauloye (1958), Gastaut *et al.* (1959) and Low (1959) that mental improvement only occurs if treatment is started within a few weeks of the onset of spasms. Only one of our four patients who showed significant mental improvement was treated within one month of the onset. Six other patients treated within three months showed no improvement. There is therefore no evidence from our results that early treatment is necessarily important.

There is definite evidence that mental retardation is not an inevitable accompaniment of infantile spasms untreated with steroids (Burnett, Gibbs and Gibbs, 1958; Jeavons and Bower, 1961) and the question arises as to whether the treatment given to our patients played any part in the mental improvement. Only two patients have achieved normal or near-normal mentality as yet. In our series of 30 patients not treated with corticotrophin or prednisolone there were two patients who, although not assessed on the Griffiths scale, appeared to be mentally normal during the second year of life, and have subsequently remained so. There is, therefore, no proof from a comparison of the two series that mental improvement, when it occurs after hormone administration, is due to the treatment. We have recently observed three other patients whose spasms ceased spontaneously before treatment could be given. They are now, at 14, 17 and 22 months of age, within the normal range, having D.Q.s over 80. On the other hand, the initial E.E.G. of C.1, the patient in the cryptogenic group who was treated within one month of onset and who now has a normal or near-normal mental level was grossly chaotic (score 22; Fig. 1), whereas the initial scores of four of the five untreated normal patients were low (4, 5, 4, 2). Moreover, his mental regression at the onset was obviously greater than theirs. This might mean that without steroids he would have continued with spasms and an abnormal E.E.G. for some time and have remained mentally defective, but this is impossible to prove. (The fifth untreated patient who is now mentally normal had two hypsarrhythmic E.E.G.s (score 15) initially.) Several patients showed a slight tendency towards mental improvement after spasms had stopped, but again this cannot be ascribed to treatment, for such a tendency to improve occurred in the series of untreated patients.

Mechanism of Action of Corticotrophin and Adrenal Steroids. The mechanism is unknown. The following hypotheses are worth consideration, but it is admitted that there is as yet no proof of their validity.

(1) Correction of Faulty Enzymatic Processes. Although a vague concept, some recent work suggests that there is in this syndrome a fault in cerebral biochemical processes. Cochrane (1959) has reported abnormal results when the tryptophan load test (Bessey, Adam and Hansen, 1957) was used in five patients with infantile spasms; pyridoxine produced mental improvement, stopped the spasms and subsequent tryptophan load tests gave normal results. We have therefore used the test in three of our patients before and during steroid treatment. In all three the results were abnormal before treatment and normal during treatment, when clinical and E.E.G. improvement had occurred. If these findings can be confirmed, it will be tempting to postulate that steroids act by accelerating the maturation of some biochemical process which is necessary for normal mental development and which inhibits epileptic discharges. The nature of the improvement affords some support for this concept. We have been impressed by the similarity between the pattern of clinical and E.E.G. improvement occurring in treated cases over a few weeks and that occurring in untreated cases over several years. In particular, the E.E.G. changes in the two groups are identical. Low (1958) and Armstrong (1959) have suggested that corticotrophin acts by accelerating maturation of enzyme systems.

(2) Changes in the Intracellular–Extracellular Electrolyte Ratios. It is known that the normal axon sheath excludes sodium from the nerve fibre and maintains a high intracellular potassium concentration; this state of affairs is temporarily reversed by the passage of a nerve impulse (Marshall, 1959). Possibly this pump action of the cell membrane is disturbed in epilepsy, and steroids restore its integrity, thus inhibiting the disordered electrical activity which is found particularly in infantile spasms. Evidence from

animal experiments (Millichap, 1958) suggests that the epileptic threshold for febrile convulsions is lower when the intracellular potassium of the brain is low. We can offer no evidence to support this hypothesis but, unlike the first hypothesis, it would explain the fact that improvement occurs in the symptomatic as well as in the cryptogenic group and also the finding of clinical and E.E.G. improvement during corticotrophin administration in major and minor epilepsy in older children (Klein and Livingston, 1950).

(3) ANTI-INFLAMMATORY ACTION. It has been suggested by Gastaut and Roger (1953) and Gibbs and Gibbs (1952) that this syndrome is due, at least in some cases, to encephalitis, allergic or otherwise. The beneficial effect of hormones would then be due to their anti-inflammatory action. However, pathological examination shows no evidence of encephalitis (Poser, 1959) and the improvement in cases where the disorder is due to other causes (perinatal brain damage, cerebral agenesis with absence of corpus callosum, and phenylketonuria) makes this hypothesis unsatisfactory.

(4) CORRECTION OF HYPOGLYCAEMIA OR LOW INTRACELLULAR GLUCOSE. There was no demonstrable hypoglycaemia in any of our patients, nor did Low (1958) find any evidence of it in his cases. It might be argued that the hormones act by increasing the availability of glucose to the cell, but this again seems an unlikely explanation of the benefit which occurred in the symptomatic group.

Recommendations. Since spasms are controlled in nearly all cases regardless of aetiology, there is some justification for using corticotrophin or prednisolone in any patient with this disorder. However, the best long-term results are obtained in the cryptogenic group, and we would not necessarily recommend treatment of every patient in the symptomatic group owing to the high relapse rate in such patients and the evidence that mental improvement is unlikely.

Treatment should be given to any patient with the disorder who does not have a definite history of perinatal or prenatal brain injury and whose previous development has been normal or nearly so. There is a fair chance of stopping spasms permanently and we agree with Stamps *et al.* (1959) that it is difficult to predict which patients will respond. We have no proof from our trial that mental improvement, when it occurs, is due to the drugs, but there is no other treatment which seems as likely to bring it about. We recommend that treatment should be given as early as possible, although again we have as yet no proof that this is essential to achieve normal mentality. Certainly we cannot be satisfied with the results presented in this paper and we feel strongly that intensive efforts to diagnose and treat the condition earlier are needed.

We now prefer corticotrophin to prednisolone as the initial drug. However, it may be justifiable particularly where long-term treatment is needed, to follow the first course with prednisolone, which can be conveniently given at home. Dumermuth (1959) recommends intermittent hydrocortisone therapy for at least six months. The daily dose of corticotrophin should be at least 25 i.u., except possibly in the first three months of life, and it may be necessary to increase the dose if there is an inadequate response. The minimum length of treatment should be one month but improvement may not occur until after this period (Case C.9). We feel that the best method of assessing improvement is by the use of the E.E.G., and a normal or non-epileptic record during treatment should be the aim. It is not necessary to use our rather elaborate scoring system to recognize improvement, but it gives a more objective assessment. Ideally an E.E.G. should be taken twice weekly but a weekly assessment may suffice. Probably the drug should be continued at full dosage for two or three weeks after a normal E.E.G. has been obtained or all chaos has disappeared from the record. The dose may then be gradually reduced. Side effects of treatment were minor (moon-face and water retention) except in one child who developed cardiac failure.

Summary

Twenty-three children with infantile spasms were treated with corticotrophin or prednisolone for at least four weeks. Spasms ceased during treatment in 18 patients but recurred in 13 after treatment.

Some E.E.G. improvement occurred in all patients except one, and a non-epileptic record was achieved in nine, though relapse occurred in five of those whose spasms recurred. Eight were given a second course of treatment but seven again relapsed.

At the end of an average follow-up period of eight months, 11 patients had no spasms.

The effect of corticotrophin was similar to that of prednisolone, although, with the doses employed, corticotrophin appears preferable. No immediate mental improvement occurred, and only two cases eventually achieved a development quotient of 80 or more. Although the drugs had a temporary beneficial effect in both the symptomatic and cryptogenic groups, better results were achieved in the latter group.

A comparison is made with a group of patients not treated with hormones and it is concluded that on the whole these drugs have a long-term beneficial effect on the spasms, whereas their effect on mentality is doubtful.

It is possible that under hormonal treatment there is an acceleration of the natural changes which occur with age. The mode of action is discussed and recommendations for treatment are made.

Thanks are due to the consultant physicians of the Children's Hospital and the consultant paediatricians of the Birmingham and Oxford Regions for allowing us to investigate and treat their patients; to Professor D. V. Hubble for encouragement and advice; to Dr. B. S. B. Wood for help with Griffiths testing, and for advice; and to Miss Doris Campbell and Mrs. S. Rickards for their patience and skill in the E.E.G. examination of these difficult patients.

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THE REPRODUCTIVE HISTORIES OF MOTHERS OF PATIENTS SUFFERING FROM CONGENITAL DIPLEGIA

BY

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The aetiology of congenital cerebral diplegia has been controversial since the earliest medical interest in the condition. Some authors have considered birth injury to be directly causal in the majority of patients (Little, 1862; McNutt, 1885; Gowers, 1888). Others have postulated the existence of some underlying intrinsic abnormality of maternal reproductive capacity causing both disorders of parturition and abnormalities of the foetus (Freud, 1897; Collier, 1899; 1923). Penrose (1938) suggested that diplegia with mental defect might be the result of a Mendelian recessive gene which could also be manifest as true microcephaly without diplegia.

The present study describes investigations into the reproductive histories of mothers in two series of diplegic patients, which aimed at discovering whether their reproductive capacity was impaired or not.

Terminology and Classification of Patients

By 'diplegia' is understood a more or less symmetrical paresis of cerebral origin, more severe in the lower limbs than the upper and dating from birth or shortly afterwards. The legs and pelvis are underdeveloped. Mental defect, epilepsy and strabismus are commonly found. The category excludes patients in whom involuntary movements or ataxia are marked clinical features. Diplegic patients may be further classified according to the state of muscle tone in the affected limbs, the extent of limb involvement and its severity (Balf and Ingram, 1955). Patients with diplegia of postnatal onset were excluded from the series.

Selection of Patients and Methods of Study

Two series of mothers were studied, the first (Series A) consisted of 78 mothers of 79 diplegic patients (there being one pair of affected identical twins). Three other patients were one of twins. These patients were born between 1938 and 1952 and were living in Edinburgh in 1952 to 1953 when a survey of cerebral palsy amongst children in the city was undertaken. Forty-nine of the patients were boys and 30 were girls. Their cerebral palsy was actively ascertained in a number of different ways and it is probable that this series of patients is representative of children suffering from congenital diplegia in the community (Ingram, 1955). Detailed family, birth, developmental and medical histories were taken from the mothers. Questions about the course of other pregnancies, the health of the patients' sibs, and the mothers' own health were asked specifically. Maternity hospital notes of the patients and their sibs were obtained, when available, to supplement information given by the mother. The sibs were inspected wherever possible and if there was any suspicion of congenital malformation or neurological abnormality they were examined if permission was given. Unfortunately the study of the mothers' reproductive histories was incomplete. The investigator neglected, for example, to obtain the date of the parents' marriage and full details of mothers' contraceptive habits or menstrual histories in many cases. Nevertheless, the results of the investigation suggested that the mothers of diplegic patients were relatively infertile, had many abnormal pregnancies, labours and deliveries and produced relatively few healthy offspring of average intelligence (Ingram, 1959).

In order to confirm these findings and to remedy deficiencies in the earlier investigation a further, larger series of 200 mothers with children suffering from congenital diplegia was studied (Series B). The patients were consecutive referrals from all parts of Scotland, suffering from congenital diplegia who had been sent to the Edinburgh Clinic of the Scottish Council for the Care of Spastics between 1945 and 1959. One hundred and seventeen were male, 83 were female and 20 (10%) of the patients were one of twins. Their ages ranged from 13 months to 30 years at the time of the survey, but two-thirds were between 5 and 15 years of age. Many children were referred because they were felt to be suitable for Westerlea (a school for spastics

catering for patients with relatively high intelligence); others because their parents were well-informed people anxious to bring their offspring for examination in Edinburgh. Thus the patients tended to be preselected by social class, intelligence and probably other characteristics. They did not form a representative group of diplegic children drawn from the community.

At the clinic, parents and patients were interviewed by a social worker, paediatrician, psychologist, and orthopaedic surgeon. Detailed accounts of family, birth, developmental and medical history were obtained and the patients examined. The records of the clinic were available to the investigator who supplemented them by reference to hospital notes describing the births and hospital admissions of patients and their sibs, by personal interviews with parents and relatives and by her own examination of the patients. In 150 instances patients and their parents were seen in their own homes. In the remainder, either information in the case notes was adequate or the patients had emigrated or lived in very remote parts of the country. In the latter group questionnaires were utilized. Since this study was predominantly concerned with maternal factors in the aetiology of diplegia other members of the families of patients were not examined.

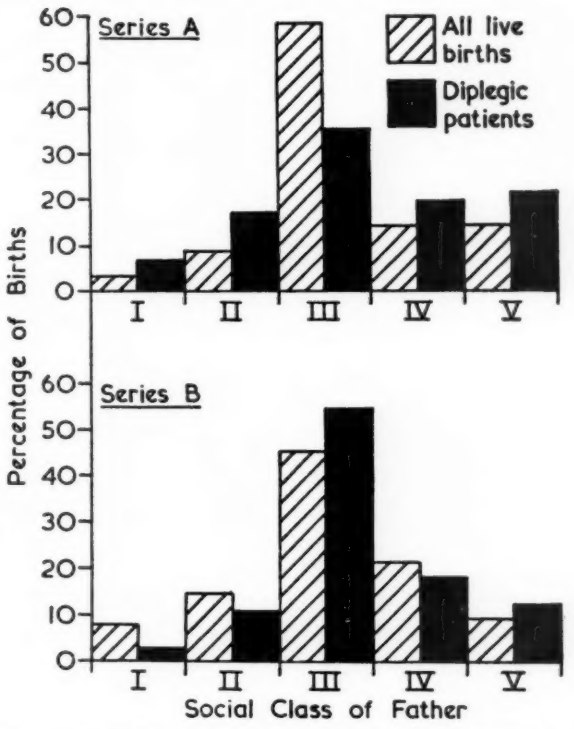

FIG. 1.—Comparison of percentage distribution of patients by social class. Patients in Series A are compared with live births in Counties of Cities in Scotland, 1951. Patients in Series B are compared with all live births in Scotland, 1951.

Results of the Investigations

Social Class. The distribution of patients by social class of their fathers compared to that of all live births in Scottish Counties of Cities, 1951, is shown in Fig. 1 (Registrar General for Scotland, 1951). In series A there was an excess of patients in social classes I, II, IV and V at the expense of social class III, compared to all live births, differences of distribution which are of statistical significance ($p < 0{\cdot}05$). In series B there was also an excess of patients in social classes I and II at the expense of III, but no excess in the combined classes IV and V. The difference between the series was probably largely the result of the parents of patients in social classes IV and V not taking their offspring to be examined so readily as those in classes I and II.

Birth Rank of Patients. The proportion of patients suffering from diplegia in each birth rank was compared to the expected proportion, taking into consideration family size. In series A, no statistically significant differences in the distribution of patients by birth rank were found. In series B, however, a significantly higher proportion of diplegic patients were first-born than would be expected ($p < 0{\cdot}01$). This may represent an actual increased liability for the first-born child to suffer from diplegia or it may merely reflect a tendency for parents to refer their first-born diplegic children more readily than those born later.

Maternal Age. The distribution of mothers in series B by age at marriage was compared to that for mothers in the general population of Scotland (Registrar General for Scotland, 1951). There is a tendency for the age at marriage to be greater in mothers of diplegic children, the maximum marriage rate occurring in the age group 25-29 years, whereas the rate in the general population is highest between the ages of 21 and 24 years. The older age of marriage of the mothers of diplegic children may be partly a reflection of the relatively high proportion of fathers in social classes I and II, in which marriage tends to occur later than in the other social classes.

Maternal age at the time of the birth of the patients in both series was studied and compared to the age of mothers of all live births in Scotland in 1951 (Fig. 2). In both series there are more mothers over 30 years of age than under, whereas the majority of mothers of live births in 1951 were under 30 years. In both series, the peak distribution of mothers by age occurs between 30 and 35 years,

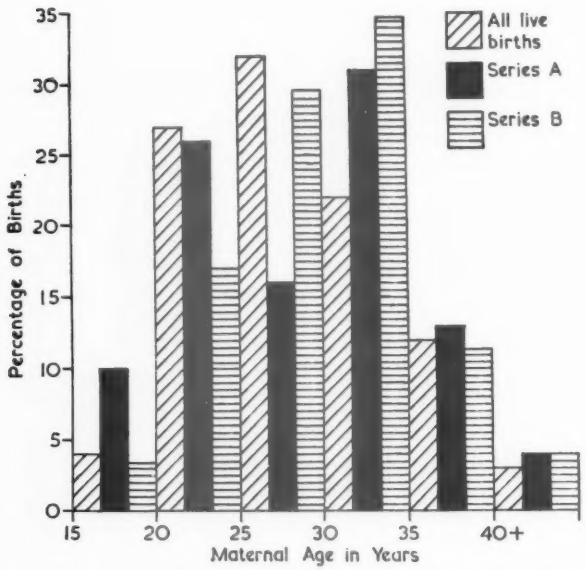

FIG. 2.—Distribution, by maternal age at delivery, of 77 patients in Series A, and 198 in Series B, compared to that for all live births in Scotland, 1951.

whereas the peak distribution of mothers in the Scottish population is in the age range 25-30 years. There is one striking difference between the two series. Whereas there is a significant excess of mothers under the age of 20 years compared to mothers in the general population in series A, this is not found in series B. This difference is probably related to the fact that a higher proportion of mothers in series A were in social classes IV and V (in which maternal age tends to be low) than mothers in series B or mothers in the general population.

Maternal Health and Menstrual History. The methods of the investigation could not give a complete picture of the health of mothers of the patients in either series though some information was obtained (Table 1). In series A 20% of the mothers and in series B 19% were considered to be unhealthy. In series B, 161 mothers were asked about their menstrual history. The average age of the menarche was 13·5 years, a figure very similar to that of Edinburgh women (13·35 years) studied by Provis and Ellis (1955). Menstrual irregularities were reported by only nine of the 161 mothers, findings which do not suggest that menstrual abnormalities occur frequently.

TABLE 1

PHYSICAL DISORDERS AMONGST 78 MOTHERS OF DIPLEGIC PATIENTS IN SERIES A AND 170 MOTHERS IN SERIES B

Disorder	Series A	Series B
Chronic infections	7	10
Chronic anaemia	0	3
Chronic nephritis	0	1
Cardiac disorders	0	5
Gynaecological disorders requiring operation	4	4
Carcinoma of breast	0	1
Thyrotoxicosis	2	0
Obesity	0	3
Menopausal symptoms	0	5
Obesity and menopausal symptoms	3	1
Total	16 or 20·5%	33 or 19·4%

Birth Rates of Mothers of Diplegic Patients. Average birth rates were calculated for married women in both series and were found to be 129·5 per 1,000 in series A and 128·1 per 1,000 in series B. The figures were compared to those given by the Registrar General in 1951 for married women of comparable age in comparable communities (Table 2). The average birth rate given for married women in the general population of Scotland (1951) was 132·2 per 1,000, and for married women in Scottish Counties of Cities (1951) was 126·8 per 1,000. Married women in the general population, however, include a significant proportion who are childless, probably about 15% in Scotland (Registrar General for Scotland, 1951). If the proportion were excluded, the rates would be 155·3 and 149·4 per 1,000 respectively, indicating that mothers of diplegic children are relatively infertile compared to married women in the general population who have borne children.

A comparison was also made between the average numbers of live and stillbirths to mothers of diplegic patients at the time of the surveys and the average number of deliveries to married women having live and stillbirths in 1951. At the time of the surveys the mothers in series A and B had an average age of over 36 years and the majority could be considered to have completed their families. In contrast, the mothers in the general population had an average age of between 25 and 30 years in 1951, yet the average numbers of live and stillbirths of mothers of diplegic patients were only slightly higher (Table 2).

The smaller number of live and stillbirths was due only in part to deliberate restriction of family size following the birth of the diplegic child, for the average number of preceding deliveries was also smaller than the average number that preceded live and stillbirths in Scotland in 1951.

The Spacing of Pregnancies. The smaller number of live and stillbirths before the delivery of the

diplegic child was not due to any longer delay in conceiving after marriage in series B. Mothers in this group gave birth to their first live or stillbirth 26 months after marriage, on average, compared to 29 months for all married mothers in Scotland giving birth in 1951. In series B, the proportion of first births taking place within the first year of marriage (48·5%) was a little higher than the proportion (40%) to married mothers in the general population in 1951.

The spacing of pregnancies, irrespective of their outcome, was studied. The intervals between pregnancies were measured from the time of delivery or abortion. The average time elapsing between pregnancies was found to be greater than that which elapsed between the pregnancies of mothers of children suffering from other types of cerebral palsy (Table 3). There was a tendency in both series for pregnancies following the birth of the diplegic patient to be rather more widely spaced than those which preceded this birth. This difference in timing may be partly the result of increase in maternal age and decrease in fertility and partly due to contraception following the birth of an abnormal child. The most striking finding was that the lapse of time between the birth of the patient and the immediately preceding and subsequent pregnancies was very great when compared to the period between more remote previous and subsequent pregnancies. The mothers of patients with congenital and acquired hemiplegia showed the same tendency for contiguous pregnancies to be more widely spaced than remote pregnancies, but the differences were much less marked than with mothers of diplegic children (Table 3).

When the timing of abortions alone was considered an interesting distribution was found. More than half the abortions in both series took place immediately before or immediately after the pregnancy resulting in the birth of the diplegic child. This distribution is significantly different statistically from that expected.

Contraception. In series B, 148 married mothers who were living with their husbands were asked about their contraceptive practices. Only 6·1% practised contraception in order to influence the spacing of their pregnancies, both before as well as after the birth of the diplegic child. Contraception was employed by 15·5% of parents only subsequent to the birth of the affected child. From these figures it is evident that contraception can only be incriminated in a minority of cases as a cause of the limited reproductive capacity of mothers of diplegic children.

TABLE 2

COMPARISON OF AGES, AVERAGE NUMBERS OF OFFSPRING AND BIRTH RATES OF DIPLEGIC PATIENTS AND MOTHERS IN THE GENERAL POPULATION OF SCOTLAND HAVING LIVE OR STILLBIRTHS IN 1951 (REGISTRAR GENERAL FOR SCOTLAND)

	Series A	Series B	Scotland, 1951	Scottish Counties of Cities 1951
Average age (in yrs) of mothers at time of study	36	40	25-30	25-30
Average number of live and stillbirths at time of study ..	2·6	2·8	2·5	—
Average age (in yrs) at birth of patients or live and stillbirths in 1951 ..	29	29	25-30	25-30
Average number of surviving and stillborn offspring before birth of patients or children born in 1951	1·0	1·2	1·5	—
Birth rate per 1,000 married women aged between 16 and 44 years ..	129·5	128·1	132·2	126·8

TABLE 3

AVERAGE NUMBER OF MONTHS ELAPSING BETWEEN TERMINATION OF PREGNANCIES (INCLUDING ABORTIONS) BEFORE AND AFTER BIRTH OF DIPLEGIC AND HEMIPLEGIC PATIENTS

	Series A	Series B	Acquired Hemiplegia	Congenital Hemiplegia
Number of mothers with pregnancies other than that resulting in birth of patient ..	62	157	50	50
Number of pregnancies before birth of patient	71	243	84	54
Number of pregnancies after birth of patient	59	181	66	51
Average period (in mths) elapsing between remote pregnancies before birth of patient ..	28	27·5	27	24
Average period (in mths) elapsing between immediate previous pregnancy and birth of patient	34	41	43	32
Average period elapsing between birth of patient and immediately subsequent pregnancy	34	40	40	37
Average period elapsing between remote subsequent pregnancies ..	20	31·5	31	27

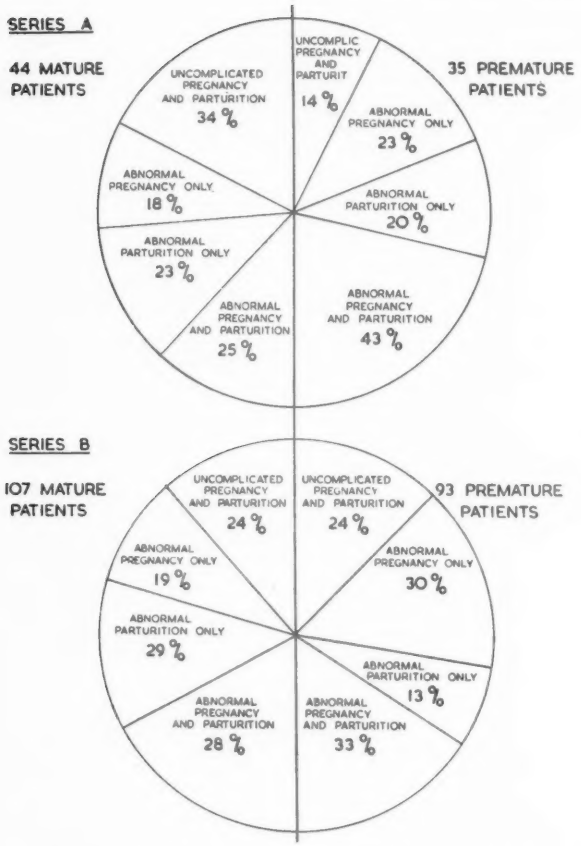
SERIES A
44 MATURE PATIENTS
35 PREMATURE PATIENTS
UNCOMPLICATED PREGNANCY AND PARTURITION 34 %
UNCOMPLIC PREGNANCY AND PARTURIT 14 %
ABNORMAL PREGNANCY ONLY 23 %
ABNORMAL PARTURITION ONLY 20 %
ABNORMAL PREGNANCY AND PARTURITION 43 %
ABNORMAL PREGNANCY AND PARTURITION 25 %
ABNORMAL PARTURITION ONLY 23 %
ABNORMAL PREGNANCY ONLY 18 %
SERIES B
107 MATURE PATIENTS
93 PREMATURE PATIENTS
UNCOMPLICATED PREGNANCY AND PARTURITION 24 %
UNCOMPLICATED PREGNANCY AND PARTURITION 24 %
ABNORMAL PREGNANCY ONLY 30 %
ABNORMAL PARTURITION ONLY 13 %
ABNORMAL PREGNANCY AND PARTURITION 33 %
ABNORMAL PREGNANCY AND PARTURITION 28 %
ABNORMAL PARTURITION ONLY 29 %
ABNORMAL PREGNANCY ONLY 19 %

FIG. 3.—Abnormalities of the pregnancies, labours and deliveries resulting in the birth of diplegic patients.

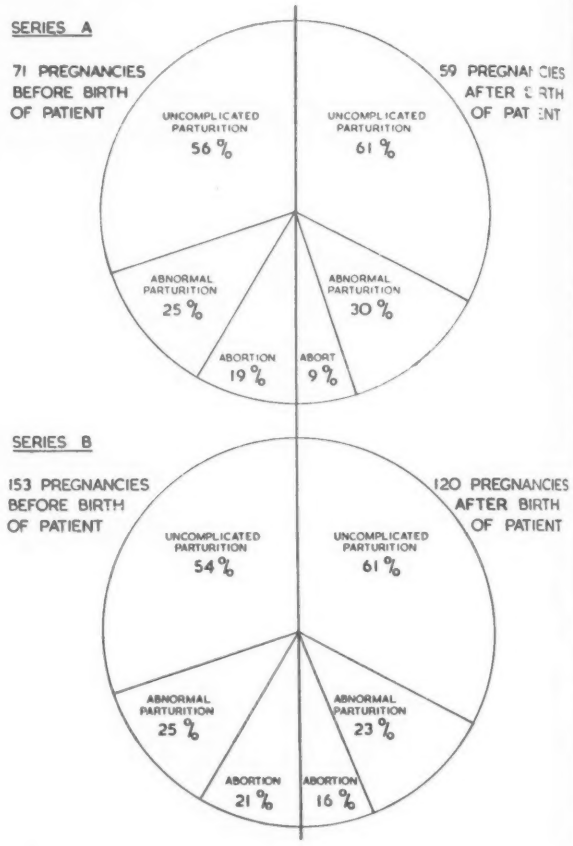
SERIES A
71 PREGNANCIES BEFORE BIRTH OF PATIENT
59 PREGNANCIES AFTER BIRTH OF PATIENT
UNCOMPLICATED PARTURITION 56 %
UNCOMPLICATED PARTURITION 61 %
ABNORMAL PARTURITION 25 %
ABNORMAL PARTURITION 30 %
ABORTION 19 %
ABORT 9 %
SERIES B
153 PREGNANCIES BEFORE BIRTH OF PATIENT
120 PREGNANCIES AFTER BIRTH OF PATIENT
UNCOMPLICATED PARTURITION 54 %
UNCOMPLICATED PARTURITION 61 %
ABNORMAL PARTURITION 25 %
ABNORMAL PARTURITION 23 %
ABORTION 21 %
ABORTION 16 %

FIG. 4.—The proportion of abnormal pregnancies before and after the births of diplegic patients.

Pregnancies Resulting in the Birth of Diplegic Patients. The pregnancies and deliveries resulting in the birth of the diplegic child were more often complicated than the mothers' other pregnancies. Nevertheless a considerable proportion of diplegic patients were born after normal pregnancies. Taking both series together, between one quarter and one third of pregnancies resulting in diplegic patients showed no abnormality apart from premature birth.

Pregnancy, labour and delivery were considered separately and the proportion of abnormalities in each was noted (Fig. 3).

The Other Pregnancies of Mothers of Diplegic Patients. Mothers in both series had a high proportion of disordered pregnancies, labours and deliveries not only with the patient but also with prior and subsequent conceptions. Only 53% of the multiparous mothers in series A and 50% in series B had other pregnancies, labours and deliveries which were all normal. The commonest abnormalities of pregnancy and parturition in both series were threatened abortion, pre-eclampsia, antepartum haemorrhage, prolonged labour, forceps delivery, breech extraction and premature birth, several of which occurred in association in many cases. No particular abnormality occurred strikingly often, relative to the incidence of the other disorders, but approximately 12% of all pregnancies in both series (other than those ending in abortion) resulted in the birth of premature infants. Pregnancies before and after the birth of the diplegic patients were separately analysed for abnormalities but no statistically significant differences were found. In both series between one quarter and one third of all pregnancies, labours and deliveries (other than those which terminated in abortion or in the birth of diplegic patients) were abnormal. When abortions are included, between one third and one half of other pregnancies were complicated (Fig. 4).

The Fate of all Conceptions of Mothers of Diplegic Patients. The fate of all the known conceptions of mothers in both series was studied. It was found

that a high proportion of them failed to result in the birth of healthy offspring, of average intelligence who survived the first year of life (Fig. 5). In both series, about 10% of conceptions ended in abortion. The combined stillbirth and infant mortality rate in series A was similar to that for the population in Scotland in 1951, but the combined rate in series B was almost twice as great in spite of the fact that so many mothers were in the social classes I and II (Table 4).

From Fig. 5 it will be seen that in both series about half the offspring who survived infancy were abnormal, the majority comprising the diplegic patients. A considerable proportion of live born sibs suffered from mental and neurological abnormalities and developmental malformations, although full details about them were impossible to obtain.

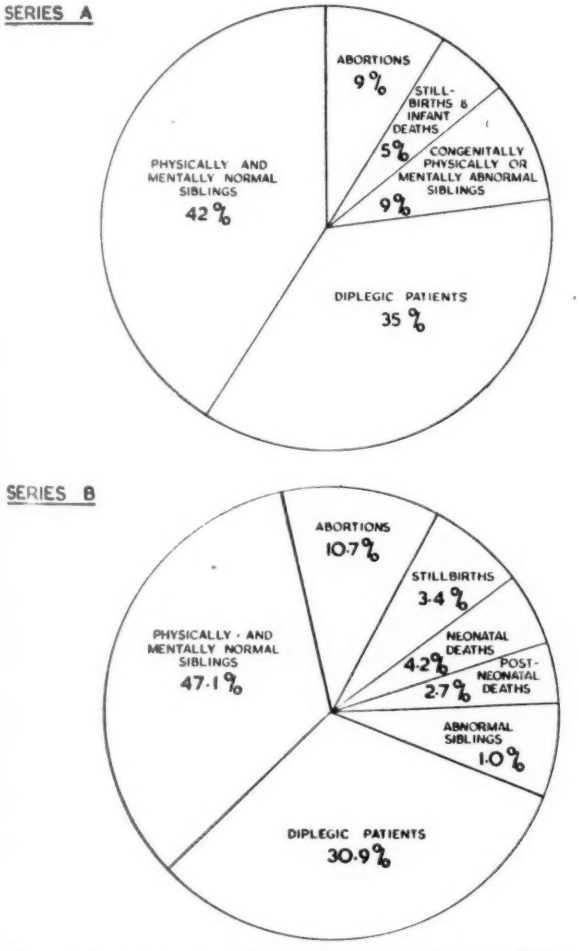

FIG. 5.—The results of 214 conceptions to 75 mothers of children suffering from diplegia in Series A and 646 conceptions to 200 mothers in Series B.

The available information about both live and dead sibs is summarized in Table 5. In series A two sibs suffered from cerebral palsy, neither of them being diplegic; in series B one sib suffered from diplegia and two from other kinds of cerebral palsy.

It was interesting to find that there was no significant difference in the proportion of abnormal pregnancies, labours and deliveries resulting in the birth of normal sibs and those resulting in the birth of abnormal sibs including those who died in infancy.

When the conceptions which ended in abortion, stillbirth, infant death, and the birth of patients and their abnormal sibs are subtracted from the total conceptions, it is found that, in neither series did more than half result in the birth of healthy children of average intelligence. These figures represent a high foetal and infant casualty rate.

TABLE 4

COMBINED STILLBIRTH, NEONATAL AND POST-NEONATAL DEATH RATES, BY SOCIAL CLASS OF OFFSPRING OF MOTHERS IN SERIES A COMPARED WITH ALL LIVE AND STILLBIRTHS IN SCOTLAND, 1951

Death Rates	Social Class		
	I and II	III	IV and V
Series A. Combined rate per 1,000 live and stillbirths ..	84·1	124·5	129·4
Combined rate per 1,000 live and stillbirths in Scotland, 1951 ..	42·5	64·5	76·5

TABLE 5

CONGENITAL ABNORMALITIES OF LIVING SIBLINGS OF DIPLEGIC PATIENTS, AND CAUSES OF DEATH OF SIBLINGS DYING IN THE FIRST YEAR OF LIFE

Condition	Series A	Series B
Surviving siblings		
Cerebral palsy	2*	3
Epilepsy	2	1
Mental retardation	11	Not known
Mongolism	0	2
Other malformations	2	3
Siblings who died neonatally		
Spina bifida	1	0
Multiple congenital deformities ..	1	0
Convulsions and cerebral haemorrhage	2	1
'Prematurity'	2	15
Infections	0	2
Unknown causes	0	8
Total	6	26
Siblings who died post-neonatally		
Febrile convulsions	3	3
Meningitis	0	2
Encephalitis	1	1
Spina bifida	0	2
Congenital heart disease	0	1
Other and unknown causes	0	3
Total	4	17
Total live born siblings	193	358

* Excluding identical diplegic twins.

Discussion

Underlying abnormalities of maternal reproductive capacity which might be responsible for abnormalities of the foetus and abnormalities of parturition were postulated as the cause of diplegia in a proportion of cases by Freud (1897). Arguments based on the clinical and pathological findings to support this theory were offered vehemently by Collier (1899, 1923). He was impressed by the remarkable symmetry of the neurological abnormalities, the pathological appearances, and by the frequency with which associated malformations were observed. He felt that 'diplegia' was more likely to be the result of either intrinsic failures of neuronal development or of processes of neuronal degeneration, than to be directly attributable to birth injury. A somewhat similar argument in favour of diplegia being due to cerebral maldevelopment more often than to birth injury was presented by Yannet (1944). Stewart, however, emphasized the diversity of pathological appearances and thought that different aetiological agents were probably important in different patients though he thought that Collier's explanations were valid for a considerable proportion of cases (Stewart, 1942). Recent studies have attempted to define two groups of diplegic patients. First, those with relatively uncomplicated paraplegia who tend to be born prematurely after pregnancies, labours and deliveries which were not disordered; second, patients with complicated diplegia (triplegia or tetraplegia), often with mental retardation and epilepsy who were more often born at term after disordered parturition (Childs and Evans, 1954; Polani, 1958, 1959; Russell, 1960). There appear to have been remarkably few attempts to discover if the mothers of diplegic patients do, in fact, show evidence of underlying abnormalities of reproductive capacity.

The findings in the present investigations support the thesis that mothers of diplegic patients may have underlying abnormalities of reproductive capacity. These are manifest in the paucity of their conceptions, the frequency with which there were disorders of pregnancy, labour and delivery and their tendency to produce poor quality or malformed offspring, many of whom died in infancy. The abnormalities of the offspring could not be related consistently to abnormalities of parturition for their pregnancies, labours and deliveries were no more often disordered than those of healthy sibs.

There is some evidence to suggest that the effects of possible underlying abnormalities of reproductive capacity are greater at the time of gestation of the diplegic patients than at other times. The periods of infertility immediately before and immediately after the birth of the diplegic child are greater than the periods which elapse between more remote previous and subsequent pregnancies. More of the contiguous conceptions end in abortion or are otherwise disordered than are pregnancies, labours and deliveries which are more remote.

The finding of a period of particularly impaired reproductive capacity at about the time of birth of the diplegic child allows a different interpretation than the usual one of high incidence of abnormal pregnancy and parturition resulting in the birth of diplegic patients. The temporary increase in the severity of the effects of the underlying abnormalities of reproductive capacity might be expected to result in a higher incidence of disordered parturition and also in a higher incidence of foetal abnormality. Therefore foetal abnormality (in this case, diplegia) and abnormal parturition would be likely to occur more frequently than in periods of greater fertility. On the other hand they would not be expected to be present together in all cases, for in some only parturition would be affected and in others the foetus would be abnormal but parturition uncomplicated. It seems easier to explain the quarter to one third of normal pregnancies, labours and deliveries resulting in the birth of diplegic patients in this way than to assume that severe birth injury occurred in them all, without clinical abnormality of parturition being apparent.

It is possible, however, to suggest a number of other interpretations of the findings. The underlying defect of reproductive capacity may not affect the foetus by causing diplegia directly. The effect may be to predispose the child to suffer arrest of cerebral development or neuronal fall out, should the natal or postnatal environment be the least unfavourable. Thus minor degrees of natal or postnatal hypoxia, which would not be damaging to normal healthy infants might cause marked brain damage in those who had been predisposed. It is possible to postulate that there are cases in which the foetus is only mildly predisposed to suffer from arrest of cerebral development or neuronal degeneration. In these, gross hypoxia or trauma during parturition would be required to cause brain damage. In more severely predisposed patients, however, relatively slight hypoxia or trauma during birth might be sufficient to cause cerebral abnormalities. Unfortunately it is possible only to speculate about the nature of these predisposing factors.

The nature and mechanisms of action of abnormalities of maternal reproductive capacity are also obscure. High maternal age is certainly important in causing diminished fertility, an increased prevalence of abnormalities of pregnancy and par-

tur tion and an increased incidence of foetal malfor nation (Murphy, 1940). A number of chronic illnesses, notably diabetes, thyrotoxicosis and gynaecological disorders, diminish fertility and have been thought to be associated with an increased incidence of foetal malformation and abnormalities of parturition. One-fifth of the mothers in the Edinburgh series were found to be suffering from chronic diseases, a high proportion of which affected the reproductive system but the way in which these disorders may have acted to cause foetal abnormality and disorders of the reproductive mechanism is largely unknown. Similarly it is impossible to assess the importance of abnormalities of male reproductive function or of mutating or recessive genes in the aetiology of diplegia on the basis of the present data. It may well be that the rapidly developing methods of genetic research may make fundamental contributions in this field.

Summary

The reproductive histories of 278 mothers of diplegic patients in two series were examined. Mothers of diplegic patients were older when they married than were women in the general population of Scotland. More were over 30 years of age when they gave birth to diplegic children than expected.

Mothers of diplegic children had fewer conceptions than married child-bearing women in the population of Scotland and their pregnancies were more widely spaced. A high proportion of their pregnancies aborted or were otherwise abnormal. Many of their offspring were stillborn, died in infancy or showed neurological or other defects if they survived. Less than half the conceptions resulted in the birth of healthy offspring who survived the first year of life.

There tended to be periods of relatively decreased fertility immediately before and after the birth of patients. Pregnancies contiguous to those resulting in the birth of diplegic children were more often abnormal than those which were more remote.

The findings are thought to provide some evidence in support of the theory that underlying abnormalities of the reproductive process in mothers of diplegic children, may be responsible for both disorders of pregnancy, labour and delivery and for the production of abnormal offspring.

These investigations were made possible by the Scottish Council for the Care of Spastics who provided facilities for research including financial support. Dr. J. A. Naughton and Mr. G. A. Pollock kindly granted free access to the Council's records. We are grateful for the support and helpful advice of Professor R. W. B. Ellis during both the investigations and in the preparation of this paper. Mr. Cyril Shepley kindly made our diagrams. We have received much secretarial help from Miss B. Sinclair of the Scottish Council for the Care of Spastics.

These investigations were carried out during the tenure, by Dr. Russell, of a graduate research fellowship from the University of Edinburgh, in 1959-60 and the tenure by Dr. Ingram of a George Guthrie Research Fellowship in the University of Edinburgh in 1952-1953.

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ANTENATAL STRESS AND THE BABY'S DEVELOPMENT

BY

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There is considerable evidence of an association between experiences during pregnancy and the health of the child. Pasamanick and Knobloch (1958), for example, report that 'in a series of studies . . . we found that certain complications of pregnancy were significantly related not only to mental deficiency (Pasamanick and Lilienfeld, 1955a), but also to cerebral palsy (Lilienfeld and Pasamanick, 1955), epilepsy (Pasamanick and Lilienfeld, 1955b), reading disability (Kawi and Pasamanick, 1958), tics (Pasamanick and Kawi, 1956), and behaviour disorders of childhood (Pasamanick, Rogers and Lilienfeld, 1956).'

There is some evidence that emotional stress during pregnancy may affect the foetus. Sontag (1941) has shown a relationship between such stress and foetal activity. Retrospective studies by Stott (1957, 1958) have suggested that 'troubles' during pregnancy may be associated with the occurrence of mental retardation, mongolism and other congenital malformations, and 'non-epidemic' ill health in the first three years of life. Although the emotional and physical components of stress could not be separated, the majority of the 'troubles' reported were primarily mental.

The present investigation was planned as an exploratory prospective study of the relationship between emotional stress during pregnancy, and the condition of the baby in the first three months of extrauterine life. As the sample was small, attention was focused on growth and neuromotor development, rather than on the occurrence of relatively rare events such as death or major defects. As will be shown, the findings suggested a relationship between antenatal stress and the infant's level of motor development.

Subjects and Method

The study took place in 1959-60, in an extremely poor Durban suburb which receives a health service from the Institute of Family and Community Health. An endeavour was made to study as many as possible of the Indian women who were resident in the area until their confinement, and gave birth within a defined six-month period. As, however, many residents used other health services, or none, this attempt was only partially successful. We knew of 136 eligible women, of whom 101 (74%) were included in the study. Seven women refused, one was too ill, and the other 27 gave birth before we were able to interview them. As official records indicate that approximately 84 other women gave birth in the area during this period, the sample is not necessarily representative of the community.

The 101 women studied ranged in age from 16 to 46 years (median: 24), and in gravidity from one to 13 (median: four). Most were Hindu (84), a few being Christian (16) or Moslem (one). Most were Tamil-speaking (71), and the remainder Telegu (17), Hindi (12) or Urdu-speaking (one). They had had from nought to eight years of schooling (median: one). All but three were married. Their monthly income (per member of household) ranged from 7s. 6d. to £12 13s. (median £2 19s. 6d.). Their husbands were, for the most part, semi-skilled or skilled workers, mainly in industry; a number were unemployed or on 'short time'. Only seven of the women had worked for gain during their pregnancy. The majority had signs of malnutrition.

Each woman was interviewed by the same investigator in her third trimester; 50 in the last month of pregnancy, 33 in the second-last, and 18 in the third-last month. Set questions were asked about the woman, her home circumstances, her diet and her troubles. Appraisals of stress were subsequently based on these interviews (see below). A physical examination was performed on all but a few of the women, including an assessment of nutritional state (see below).

Forty-eight of the women were delivered at home by a midwife, and 22 in hospital. The other 31 had no skilled intranatal care. Records of delivery were not available for this latter group. A number of the babies in this group were, however, seen at home soon after birth, so that birth weights were available for a total of 83 babies.

The home was visited as soon as possible after delivery, and the neuromotor development of the baby tested (see below). Further neuromotor examinations were carried out by the same investigator at four weeks and 13 weeks after delivery. The babies' median ages at the three examinations were, respectively, 3, 32 and 93 days. At the first examination the baby's length was measured,

and at each examination the baby was weighed. A full physical examination was carried out at 13 weeks. At each contact, the mother was asked about the baby's illnesses, feeding and progress.

Practical difficulties prevented a rigid adherence to the above schedule. As there was sometimes a delay before we knew of the confinement, and as three babies died in the neonatal period, only 84 initial examinations were carried out. Subsequently one other baby died, one was adopted, and three left the area. The four-week examination was performed on all but five, and the 13-week examination on all but one, of the babies still in the sample. Of the babies whose birth weights were known, initial neuromotor examinations were conducted on 73; the major findings will relate to this group.

It proved impossible to ensure that babies were examined at identical ages. In 17% of cases the initial examination was delayed until the second week of life. The 'four-week' examination was delayed until the age of 5 weeks in 19% of cases, and until 6 weeks in 2%. The '13-week' examination was delayed until 14 weeks in 14%, 15 weeks in 9%, and still later in 5%. However, as the arrangements for examination were made without reference to the assessments of antenatal stress, this variation is unlikely to have introduced a bias; there was in fact no relationship between the degree of antenatal stress and the child's age at examination.

Full data were not available in all cases, for the reasons given above, and also because some women were unable to give definite answers (concerning, for example, household income) and occasional questions and procedures were inadvertently omitted. Such cases are omitted from the relative analyses.

In testing the statistical significance of the findings, use was made of the tables provided by Armsen (1955) or, where these were not applicable, of chi-square tests, with Yates' correction.

Antenatal Stress. Assessments of stress were based on the responses to the following questions:

How are you feeling? How have you been feeling since you became pregnant?

Since you became pregnant, have you had any illnesses, operations, accidents, shocks or frights, or worries?

Are the other members of your family well?

Is your husband in a stable job? Is his job secure?

Have you been working during your pregnancy?

Do you mind whether you have a boy or a girl?

Were you pleased when you found you were pregnant?

Have things been going smoothly in your home?

Does all go well between you and your in-laws?

Does all go well between you and your husband?

Have you any other worries?

Do you think your baby will be all right? Do you think any of these troubles may affect your baby?

Like Stott (1958), we considered it advisable to rate the woman's stress by, as far as possible, objective situational criteria. To quote Stott, 'a situation or event was rated as distress or shock-producing if this would have been its expected effect upon an emotionally stable woman'. To this end, the assessment was made some time later, on the basis of the written record, by the two investigators who had not participated in the interview. A scale of 0 to 5 was used. Typical examples were:

Assessment	Stress
1	Minimal stress: Slight abdominal pain for a week.
2	Mild stress: Husband on 'short time': unemployed for one or two days a week: no financial strain.
3	Moderate stress: Husband unemployed for three months: son is working, supplies groceries.
4	Marked stress: Husband convicted of offence: struggling to repay money borrowed to pay fine.
5	Extremely marked stress: Flooded out of house when canal burst: family had to flee for shelter.

Each circumstance which the woman had mentioned was rated in this way, and the highest rating allotted to her was taken as her stress rating. In this way the women were divided into two groups: those who had experienced moderate or major stress (ratings 3 to 5), and those who had not (0 to 2). Separate assessments were made of stress in the first four months of pregnancy, and of stress from the fifth month onward. Except where otherwise stated, the latter assessment is the one used in the analyses. There was a high correlation ($r = +0{\cdot}80$) between these ratings of stress in late pregnancy and similar ratings made by the interviewer at the time of the interview, taking into account the woman's overt expressions of stress as well as her responses.

Nutritional State. The mother's nutritional state was assessed by (*a*) rating the degree of four skin lesions (skin xerosis, phrynoderma, follicular enlargement, and dyssebacia/folliculosis) on her face, the back and front of her chest, her shoulders, upper arms and thighs; (*b*) noting the presence of selected lip, gum and tongue lesions; (*c*) measuring her arm skinfold thickness, using the Harpenden caliper (Edwards, Hammond, Healy, Tanner and Whitehouse, 1955), and height in late pregnancy, and her weight three months after delivery. The methods used have been described in detail elsewhere (Abramson, Gampel, Slome and Scotch, 1960).

The baby's nutritional state was assessed at the 13-week examination, by noting the presence of glossitis and of skin xerosis (dullness, dryness or increased reticular markings) on the face, forearms or legs.

Neuromotor Development. The test procedures fell into three groups:

(*a*) Tests of muscle tone, based on those described by Geber and Dean (1957). As the tests we selected were found to have no discriminatory value, 94-100% of the babies reacting similarly, these tests and the findings will not be detailed.

(*b*) Tests of adaptive behaviour: the 'dangling ring', 'bell-ringing', and 'rod in hand' tests (Gesell and

Amatruda, 1941). As these tests also elicited little or no variation, the findings will not be detailed.

(*c*) Tests of gross motor behaviour (Gesell and Amatruda, 1941). The following five procedures were applied and the responses rated as shown. The sum of these ratings was used as the baby's 'motor score'; the higher this score, the higher the developmental level. In occasional cases, the baby's response to a specific procedure was inadvertently left unrecorded; this applied to 1% of the individual procedures; in calculating the 'motor scores' of such babies, the missing rating was taken as 1.

(i) *Pull to sitting.* The baby was pulled by the arms from a supine to a sitting position, and the presence of head lag recorded. 0 = complete or marked lag; 1 = moderate lag; 2 = slight or no lag.

(ii) *Sitting supported.* The child was then held in the sitting position, supported by the sides of the chest, and the upper back observed. 0 = back rounded; 2 = back straight.

(iii) *Standing supported.* The baby was then held in the standing position. This test was omitted in the initial examination. 0 = slight or no resistance to table top; 1 = appreciable weight support; 2 = rises to toes.

(iv) *Prone (held).* The child was then suspended in the prone position, and the head observed. 0 = head droops; 2 = head up.

(v) *Prone on table.* The baby was then placed prone on the table, with the head turned to the midposition, and the head watched. 0 = head not raised; 1 = raised momentarily; 2 = raised for several seconds or recurrently.

Results

Relationship with Baby's Weight and Length. Babies born to women who had experienced moderate or major antenatal stress did not differ significantly in weight (at birth, 4 weeks, or 13 weeks) or in length from those born to other women. Prematurity rates (birth-weights of 5½ lb. or less) were 14% and 18% respectively.

Relationship with Baby's Motor Development. Babies born to mothers who had experienced moderate or major stress tended to have lower 'motor scores' at their first examination. This tendency was, however, not statistically significant ($p < 0{\cdot}20$). A similar tendency was found in respect of three of the four separate test procedures, reaching statistical significance ($p < 0{\cdot}02$) in respect of one (the 'prone on table' test).

It was thought possible that the inclusion of babies of all birth weights might be obscuring an actual relationship, as the heavier babies might be more mature. Among babies weighing 8 lb. 0 oz. or less, there was no evidence whatever that their 'motor scores' varied with their weight. However, it was noted that of the babies who were heavier than this, none had low 'motor scores'. Although they were few in number, so that this difference was not a significant one, it was considered advisable to exclude them from the analysis. Accordingly, a separate analysis was made of the babies weighing 8 lb. 0 oz. or less at birth, i.e. excluding heavier babies and those with unknown birth-weights. It was not considered necessary to exclude the very light babies, both because they did not differ in their 'motor scores', and because it is doubtful whether in this community a very low birth weight is usually indicative of immaturity; it has been noted, for example, that although the prematurity rate is very high, the first-week mortality rate ascribed to prematurity is not high (Kark, 1957). Although studies elsewhere have shown a relationship between prematurity and disturbed neuromotor development (Drillien, 1959; Knobloch and Pasamanick, 1959a and b), this relationship is marked only among extremely small premature babies. Only two of our babies weighed under 4½ lb. at birth, and none under 3½ lb. Neuromotor examinations were carried out soon after birth on 66 babies weighing 8 lb. 0 oz. or less at birth, of whom 40 were born to mothers who had experienced moderate or major antenatal stress, and 26 to mothers with little or no stress. These groups will be referred to as the 'high-stress' and 'low-stress' groups respectively.

There were clear indications that the babies in the high-stress group were relatively backward when first examined. Seventeen of the 40 had 'motor scores' below 3, compared with four of the 26 in the other group ($p < 0{\cdot}05$). Two of the individual test procedures showed similar differences. The percentage with rounded backs when sitting supported was 33 for the high-stress group, and 7 for the low-stress group ($p < 0{\cdot}05$). The percentage who did not raise their heads when laid prone on the table was 63 for the high-stress group, and 29 for the low-stress group ($p < 0{\cdot}05$). The 'pull to sitting' test showed a similar tendency which however, fell short of significance.

A similar relationship was found at the 4-week examination of babies weighing 8 lb. 0 oz. or less at birth. Of the 38 'high-stress' babies examined, 25 were relatively backward ('motor scores' of under 8), compared with five of the 23 'low-stress' babies ($p < 0{\cdot}01$). The individual test procedures showed similar relationships, but these were not significant.

At 13 weeks, no relationships with antenatal stress were manifested, either by the 'motor score'

TABLE 1

COMPARISON OF MOTHERS UNDERGOING MODERATE OR MAJOR STRESS WITH THOSE UNDERGOING LITTLE OR NO STRESS*

	High-stress Group	Low-stress Group	p†
Age (yrs): Median	27·5	23	
Aged 30 or over (%)	38	15	<0·05
Schooling: Median (years of schooling)	0 (38)	3 (26)	
No schooling (%)	53 (38)	27 (26)	
Religion: Hindu (%)	90	85	
Home circumstances:			
No. in home: Median	6	6	
10 or more (%)	28	8	
Crowding index:‡ Median	4	3	
5 or over (%)	45	8	<0·01
Monthly income per member of household (shillings): Median	44 (34)	68 (21)	
Under 40 (%)	33 (36)	14 (22)	
Monthly food expenditure per member of household (shillings): Median	29 (31)	36 (21)	
Under 30 (%)	55 (31)	24 (21)	
Diet (no. of days per week on which item is taken):			
Meat or fish: Median	2	3	
Under 2 (%)	35	8	<0·02
Milk (as a beverage): Median	0	1	
Not taken (%)	71	40	<0·05
Fruit: Median	1	6	
Under 2 (%)	58	23	<0·02
Nutritional state:			
Skin lesions (median scores): Skin xerosis (range 1 to 27)	12 (37)	11 (25)	
Phrynoderma (range 0 to 7)	1 (37)	1 (25)	
Follicular enlargement (range 0 to 6)	0 (37)	1 (25)	
Dyssebacia/folliculosis (range 0 to 6)	1 (37)	2 (25)	
Moderate or marked mucosal lesions (%): Lips	0 (37)	4 (25)	
Gums	16 (37)	12 (25)	
Tongue	16 (37)	16 (25)	
Arm skinfold thickness (mm.): Median	10·1 (37)	9·8 (25)	
Height (in.): Median	60·5 (37)	59·5 (25)	
Weight (lb.): Median	110 (27)	101·5 (22)	
120 or over (%)	33 (27)	9 (22)	
Pregnancy:			
Work during pregnancy (%)	7	12	
Calculated gestation period (wks): Median	39 (24)	40 (19)	
Complaints of ill health (%): In first 4 months	45	46	
Later in pregnancy	75	46	<0·05
Delivery:			
Duration of second stage (min.): Median	15 (17)	15 (17)	
'Easy labour' reported by mother (%)	72 (39)	73	

* These findings relate to women whose babies weighed 8 lb. 0 oz. at birth and had a neuromotor examination in their first two weeks of life. There were 40 such women in the high-stress group, and 26 in the low-stress group. In some respects data were not available for all women; in such cases the figures are based on the number of women shown in parentheses.

† The probability that the difference may be due to chance. Stated only if under 0·05.

‡ Number in household — number of rooms used for sleeping.

or by the results of separate tests. Of the 35 'high-stress' babies examined, six had 'motor scores' of under 8; of the 26 'low-stress' babies, four.

It was considered likely that the association of antenatal stress with a low level of motor development in these subjects was a real one, and not a mere chance finding resulting from vagaries in the appraisals of stress or motor capacity. A relationship manifesting itself by the use of more than one separate test procedure, and found at two different stages in the infant's life, was considered unlikely to be an accidental artefact.

However, it was possible that the differences in motor development between the two groups were expressions, not of differences in antenatal stress, but of coincidental differences between the two groups. Accordingly, the 'high-stress' and 'low-stress' groups were compared in respect of a number of other variables. The salient findings are summarized in Tables 1 and 2. Wherever a difference was found, the role of the factor was explored by (*a*) seeking evidence of a relationship between it and the babies' initial 'motor scores', in the 'high-stress' group, in the 'low-stress' group, and in both combined; and (*b*) seeing whether the 'high-stress' babies were more backward than the 'low-stress' babies when the factor was held as constant as the small numbers of babies permitted.

Although a number of differences were in fact found between the two groups, they did not appear to be relevant to the developmental differences found. The 'high-stress' women tended, for example, to be older. However, neither among these women nor in the other group, nor in both combined, was there any suggestion of a relationship between mothers' ages and their babies' 'motor scores'. Among

TABLE 2

COMPARISON OF BABIES BORN TO MOTHERS WITH MODERATE OR MARKED STRESS, WITH THOSE BORN TO MOTHERS WITH LITTLE OR NO STRESS*

	High-stress Group	Low-stress Group	p†
Birth rank:			
Median	4·5	3	
1 or 2 (%)	15	46	0·0
Weight (lb.):			
At birth: Median	6·75	6·25	
Under 7 (%)	50	65	
At 4 weeks: Median	8·1 (38)	7·9 (22)	
Under 8·5 (%)	61 (38)	75 (22)	
At 13 weeks: Median	11·4 (35)	11·4 (25)	
Weight growth (mean increment per week (oz.)):			
Birth to 4 weeks: Median (range 0 to 10·8)	4·2 (37)	4·7 (21)	
Birth to 13 weeks: Median (range −0·3 to +10·1)	5·2 (34)	5·4 (25)	
Length at first examination (in.): Median	19	18·9	
Nutritional state at 13 weeks:			
Skin xerosis present (%)	43 (35)	44 (25)	
Glossitis present (%)	14 (35)	19 (25)	

* These findings relate to babies weighing 8 lb. 0 oz. or less at birth, who had a neuromotor examination in their first two weeks of life. There were 40 such babies in the high-stress group, and 26 in the low-stress group. In some respects data were not available for all babies; in such cases the figures are based on the number of babies shown in parentheses.

† The probability that the difference may be due to chance; stated only if it is less than 0·05.

women aged under 25, low 'motor scores' were significantly commoner ($p < 0{\cdot}05$) in the 'high-stress' group; among women aged 25 or more there was a similar difference, not significant.

Similar findings applied to other variables in respect of which the two groups differed. The 'high-stress' women tended to be of a lower educational standard, to come from more crowded and poorer homes, and to have an inferior diet. When each factor was considered in turn, findings emerged similar to those relating to maternal age.

In spite of the dietary differences, the nutritional indices used revealed no differences in the state of nutrition of the two groups, except that women in the 'high-stress' group tended to be heavier. This was probably related in part to their greater age. Using the procedures described above, no relationship could be shown between mothers' weights and their babies' 'motor scores'. The association between stress and motor retardation thus appeared to be independent of nutritional factors, with the reservation that the crude clinical measures used may not have been adequate to demonstrate actual nutritional differences.

Complaints of ill health in the latter part of pregnancy, but not in early pregnancy, were commoner in the 'high-stress' group. However, both among women with complaints and among those without, 'high-stress' babies had lower 'motor scores', significantly so in the latter group ($p < 0{\cdot}01$). It was found, however, that in the 'low-stress' group, the babies of mothers with complaints tended to have lower 'motor scores' ($p < 0{\cdot}05$); this finding did not apply to the 'high-stress' group. These findings suggested that while the developmental difference between the two groups was not accounted for solely by differences in the prevalence of maternal disorders, the presence of such disorders might have had some bearing on the baby's development. We were not able to obtain full medical records for all the women, many of whom made scanty use of health services. The few definite major complications of pregnancy which were recorded occurred in both groups.

Delivery was for the most part short, easy and uneventful in both groups. Four obstetric complications were recorded in the 'high-stress' group, and two in the 'low-stress' group.

The two groups of babies are compared in Table 2. In each group the sexes were almost equally represented. The 'high-stress' babies tended to be of a higher birth-rank; this was related to the greater age of their mothers. No evidence could be found, however, that rank was independently related to motor development. They tended also to be slightly, though not significantly, heavier at birth; this was probably a reflection of their higher birth ranks, as there was a significant relationship between rank and birth weight. As has already been stated, no relationship could be shown between birth weight and motor development, within this weight range. The two groups did not differ notably in their subsequent weight growth, in length, or in the prevalence of signs of malnutrition at the 13-week examination.

Other Relationships.

MOTHER'S ATTITUDE TO CHILD. It is recognized that experiences during pregnancy have important implications for the mother-child relationship (Caplan, 1959). Two of our findings had a bearing on this topic. First, mothers were asked, soon after delivery, 'Were you pleased you had a son (or daughter)?' Among women giving birth to daughters, their responses were significantly related to their experience of stress during pregnancy. Of 22 women exposed to antenatal stress, nine stated that they were dissatisfied with their child's sex; of 20 women with little or no stress, two ($p < 0{\cdot}05$). There was no such relationship among the mothers of sons, who tend to be preferred in this community.

Secondly, the mothers were asked, four weeks and 13 weeks after their confinement, 'Do you sometimes wish you hadn't had this baby?' Of 54 women exposed to stress in pregnancy, 13 answered 'Yes'; of 43 women exposed to little or no stress, only one answered 'Yes' ($p < 0{\cdot}01$).

INFANT FEEDING, DISORDERS AND DEATHS. Antenatal stress bore no apparent relationship to infant feeding practices; 95% of the women were still breast feeding at 13 weeks.

There was no relationship to the occurrence of illnesses in the first 13 weeks. Two babies had major congenital defects, one of whom died. The mothers of both had been exposed to stress. Three other babies died of pneumonia; the mother of one had been exposed to stress.

Causes and Timing of Stress. Almost half the women in the 'high-stress' group were exposed to more than one category of stressful situation (Table 3). The commonest circumstances causing stress were the unemployment or partial unemployment of the husband, and distress at being pregnant, usually in conjunction with straitened economic circumstances. In no case was maternal illness the sole stress to which the woman was exposed. Nine women in the group definitely experienced sudden shocks.

Although the women were classified according to their experience of stress in the latter part of their pregnancy, it could not be concluded that the relationships found were specific to late-pregnancy stress. 92% of the women in the 'low-stress' group were also exposed to little or no stress in the first four months of pregnancy, and 87% of the women in the 'high-stress' group were also subjected to moderate or marked stress in early pregnancy. In fact, when the women were classified according to their stress in early pregnancy, the same significant relationships were found with their babies' 'motor scores' as when they were grouped according to their stress in later pregnancy.

TABLE 3
CIRCUMSTANCES CAUSING STRESS

	No. of Categories in Which There is Moderate or Major Stress				
	1	2	3	4	Combined
No. of women	22	12	4	2	40
Percentage of women	55	30	10	5	100
Category:					
Husband's unemployment or job insecurity	8	7	3	2	20
Distress at being pregnant	5	9	3	1	18
Serious illness in family	3	—	2	1	6
Low income	2	3	1	—	6
Own illness	—	2	1	1	4
Marital difficulties	1	—	—	1	2
Anxiety concerning child's sex	—	1	1	—	2
Miscellaneous	3	2	1	2	9

These findings apply to the women in the 'high-stress' group.

Relation of Motor Development to Baby's Nutritional State. Although at their first examination the 'motor scores' of babies weighing 8 lb. 0 oz. or less at birth bore no relationship to their birth weights, at the subsequent examinations of these babies there was a significant association of low 'motor scores' with low weights or a low rate of weight growth (Table 4). These associations applied

TABLE 4
RELATIONSHIP BETWEEN MOTOR DEVELOPMENT AND BABY'S NUTRITIONAL STATE

	No.	Motor Development Score <8 (%)	p*
4-week examination:			
Weight (lb.): Under 8·5	38	66	0·01
8·5 or more	21	24	
Mean weight gain per week since birth (oz.): Under 3	16	75	0·05
3 or more	42	40	
13-week examination:			
Weight (lb.): Under 11	24	38	0·005†
11 or more	36	3	
Mean weight gain per week since birth (oz.):			
Under 6	37	27	0·025†
6 or more	22	0	
Skin xerosis: Present	26	27	
Absent	34	9	
Glossitis: Present	10	30	
Absent	50	14	

These findings relate to babies weighing 8 lb. 0 oz. or less at birth.
* The probability that the difference may be due to chance; stated only if it is less than 0·05.
† According to Table 8 in Fisher and Yates (1953).

both to 'high-stress' and to 'low-stress' babies, though significance was not reached in each instance. There appeared to be a similar association, not significant, between low 'motor scores' and the presence of skin xerosis or glossitis at the 13-week examination.

These findings were interpreted as indicating that if a baby's growth and nutrition were impaired, his rate of motor development was likely to be slow, whether as a direct result, or because of the action of common or related causes. As the rate of postnatal growth is largely affected by extra-uterine factors, it appeared that the tempo of motor development after birth also was largely dependent on such factors, the effect of which had by 13 weeks obscured the original association with antenatal stress. Knobloch and Pasamanick (1953) have shown a similar relationship between behavioural development and physical growth.

Discussion

The results indicate an association between antenatal stress and motor retardation, among babies weighing 8 lb. 0 oz. or less at birth. This association, which was apparent both soon after birth and at four weeks after birth, appeared to be independent of other factors associated with emotional stress in this sample.

In view of the small size of the sample, however, it would be incautious to generalize from the findings in this one group, pending their confirmation elsewhere.

It may be noteworthy that Knobloch and Pasamanick (1959b) found, in a study of the neuromotor development of babies aged 40 weeks, that their degree of neuromotor disturbance bore a positive relationship to the amount of tension shown by their mothers at that time. Although there are alternative explanations, it may be that this finding is due in part to a tendency for a pregnant woman's stress to persist after the baby has been born.

Pasamanick and his colleagues have postulated that similar antenatal processes may produce a wide variety of effects on the foetus, so that there is a 'continuum of reproductive casualty', extending from lethal to various non-lethal effects (Pasamanick and Knobloch, 1958). If confirmation of our findings is forthcoming, it may well be that slight motor retardation comprises part of such a continuum of reproductive casualty, falling into place at the extreme non-lethal end of the scale. Stott's studies, cited above, have indicated that emotional stress in pregnancy may, in some cases, have more damaging effects. It is noteworthy that figures derived from a prospective study carried out by McDonald (1958) show that of women undergoing marked anxiety or emotional shocks in the first 12 weeks of pregnancy, 7·2% subsequently had abortions, stillbirths, neonatal deaths or infants with major defects. The corresponding figure for women with no such anxiety or shocks was 5·7%. The difference between these figures was, however, not significant.

Our findings suggest that the tempo of motor development after birth is closely affected by extra-uterine conditions; by 13 weeks, the relationship with antenatal stress is no longer apparent. It may be that in less unfortunate communities, where the conditions of extra-uterine life are generally more favourable, any retardation resulting from adverse intra-uterine conditions may remain obvious until a later stage of life.

It is of little value at this stage to speculate on the possible mechanisms by which stress in the expectant mother may affect her baby's development. Not only endocrine and nervous influences, but associated nutritional factors also may play a part. Further, the limited evidence found of an association between complaints of ill health during late pregnancy and motor retardation, suggests the possibility that maternal illness may also play a part. Such complaints were significantly commoner in the 'high-stress' group, although no women were allocated to this group on the grounds of illness alone. This last finding is consistent with that of Gordon and Gordon (1957), who found a relationship between emotional disturbance and physical complications of pregnancy in a group of United States maternity patients.

It is of interest that, in so far as our evidence goes, a woman's exposure to conditions which, objectively considered, appear likely to produce emotional stress, bears relatively little relationship to her baby's development. There was no simple relationship with, for example, poverty, crowding or a poor diet. On the other hand, when the presence of stress was assessed on the basis of the woman's own report of her difficulties, a significant association with her baby's development was found. This finding parallels that of Hinkle and Wolff (1957) and their colleagues, whose intensive studies of several groups of subjects indicate that the occurrence of illness bears a closer relationship to the subjects' own perception of their life situations as being unpleasant or demanding, than to their exposure to 'objectively' adverse circumstances.

Summary

A prospective study of Indian expectant mothers in Durban revealed a relationship between emo-

tional stress during pregnancy and a low level of motor development in the infant. This association, which applied to babies weighing 8 lb. 0 oz. or less at birth, appeared to be independent of other factors associated with emotional stress. By 3 months of age this relationship was no longer apparent, as the tempo of motor development after birth appeared to be largely dependent on extra-uterine conditions.

The possible significance of these findings is discussed. It is suggested that motor retardation may form part of a continuum of reproductive casualty, and that in some cases emotional stress during pregnancy may have more far-reaching effects on the baby.

We are indebted to our subjects for their patience with us despite their misfortunes; to Professor D. Crichton for giving us access to hospital records; and to Mr. V. Zill, Mr. S. J. Maharaj and others members of the staff of the Institute of Family and Community Health.

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THE PUFF TEST

AN ATTEMPT TO ASSESS THE INTELLIGENCE OF YOUNG CHILDREN BY USE OF A CONDITIONED REFLEX

BY

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Krasnogorski (1913), who was working with Pavlov in St. Petersburg, described his experiments on establishing conditioned reflexes in children. His methods were expanded by Mateer (1918) whose paper will be described later. No further relevant work on the subject was published until Pavlov's famous book on Conditioned Reflexes (Pavlov, 1927). This work is well known and only a brief summary of it will be given here. Pavlov distinguished between inborn and conditioned reflexes. If food is placed in a dog's mouth, the dog salivates. That is an inborn reflex. If the dog salivates when he hears the footsteps of his master coming to feed him, that is a conditioned reflex. A conditioned reflex must be founded on an inborn reflex or a new stimulus can be used for a well-established conditioned reflex.

There are three components of a conditioned reflex: the unconditioned stimulus, which gives rise to the unconditioned reflex, and the conditioned stimulus which, after being paired with the unconditioned stimulus, elicits the same response. In the example given above the unconditioned stimulus is the food, the reflex the salivation and the conditioned stimulus the footsteps. When conditioning is established the reflex will appear if the conditioned stimulus alone is exhibited. Pavlov stressed that successful conditioning could only be expected under optimal circumstances. Irrelevant stimuli such as fear, noise or the desire to micturate tend to prevent the establishment of conditioned reflexes in animals. If a conditioned reflex is not periodically reinforced by the reintroduction of the unconditioned stimulus it gradually becomes extinct. This fading away of the reflex is known as deconditioning. Even after deconditioning, however, the reflex may spontaneously regenerate with the passage of time.

Pavlov's book referred only to experiments on animals, but other workers tried similar experiments on children. One of the earliest attempts to utilize the concept of the conditioned reflex in diagnosis was reported by Aldrich (1928). He conditioned pain, in the form of a pin-scratch on the sole of the foot, and the sound of a dinner gong, in order to demonstrate hearing in a 3-month-old infant.

It was found that the younger the child, the harder he was to condition. Wenger (1943) described some controlled experiments in which he tried to condition infants to blink in response to an electric shock which had been coupled with a bright light shining into their eyes. Later some of the infants blinked with the shock alone, but only after they had received up to 240 stimulations administered over several days. Even then not all the infants could be conditioned. In early infancy 100-300 paired stimulations may be required to establish a conditioned reflex, whereas by the age of 1 year, two or three stimulations will suffice (Gesell, 1948).

While there is undoubtedly a connexion between ease of conditioning and age, there has been some doubt as to whether ease of conditioning can be correlated with intelligence. Gesell and Ilg (1937), when studying the feeding behaviour in infants, noticed that normal infants became excited when they observed their food being prepared. As this occurred first at the age of about 16 weeks in normal infants, but later in mentally retarded infants, the observation has been used to assess intelligence. This is an example of a natural conditioned reflex which can be used as a developmental test. On the other hand Campbell and Hilgard (1936) using the conditioned eye-blink in 63 university students, found that there were wide individual differences in the ease with which a conditioned response could be formed. After performing intelligence tests on the students, they came to the conclusion that intelligence was not significantly related to the ease

FIG. 1.—The puff gun.

of conditioning. This work, however, is not strictly relevant as it concerns adults and the differences in intelligence found were not very great.

Birch and Demb (1959) performed some experiments on 26 mentally retarded children. The conditioned reflex they used was a mild electric shock and a light. Changes in the skin reaction were recorded by a psychogalvanometer. The children were all over 6 years of age, most of them being between 10 and 16 years old. The intelligence quotients ranged from 30-85 with an average of 50. No correlation was found between the ease of conditioning and the intelligence quotient. Kodman, Fein and Mixson (1959) have also experimented with the psychogalvanometer in mentally defective children. They concluded that further inquiry is required 'into the relationship between ease of conditioning and the learning process in severely retarded children'.

It has been shown that audiometry by means of the 'peep-show technique' (Dix and Hallpike, 1947), and by psychogalvanometry (Bordley and Hardy, 1949), both of which utilize the principle of the conditioned reflex, are of little value in testing mentally retarded children, as they cannot easily be conditioned (Statten and Wishart, 1956).

The present viewpoint can be summarized in the words of Hilliard and Kirman (1957) who wrote, 'It can be said of mongols as of other imbeciles and idiots that inborn or unconditioned reflexes are present though possibly weaker than normal. On the other hand conditioned reflexes which form the basis of adaptive behaviour are established much more slowly and less surely'.

Thus there is good evidence that conditioned reflexes can be established in young children, and that the ease with which this can be done bears some relationship to age. The evidence as to whether there is any relationship to intelligence, however, is conflicting.

The Present Experiment

The experiments described in this paper were designed to find out: (1) the relationship between the development of a conditioned reflex and age in children with normal intelligence, (2) the relationship between a conditioned reflex and both age and intelligence in mentally retarded children, and (3) whether the time taken to establish a conditioned reflex could be used as a measure of intelligence.

According to Pavlov (1927) the easiest conditioned reflexes to establish are those associated with the alimentary tract and those concerned with the prevention of injury. In babies, apart from the excitation with feed reflex mentioned above, no alimentary reflex could easily be utilized in a clinical test. I tried several methods of establishing a conditioned reflex, such as banging a gong, and stimulating the sole of the foot with a jet of cold water to obtain a withdrawal reflex, or the administration of a slight electric shock just before shining a light into the eyes to obtain a pupillary reaction. These all failed and eventually the following test was devised.

The unconditioned or inborn reflex used was the eye blink when air was puffed into the face. The conditioned stimulus was the presentation of the 'gun' without any air being puffed, and the conditioned reflex was the eye blink *before* the air was puffed.

The details which follow describe an attempt to standardize the procedure so that comparison could be made between one child and another.

Detailed Description of the Test. The apparatus used (Fig. 1) consisted of a glass tube 18 cm. in length tapered

at one end to form a nozzle (bore approximately 1 mm.) and bent 11 cm. from the end to an angle of about 110 degrees. A side hole of about 1·5 cm. diameter was made on the obtuse side of the bend. The glass tube was attached by rubber tubing to a cylinder of compressed air or oxygen which was fitted with a flow meter. When the gas was turned on it normally flowed out of the large side-hole in the glass tube (called the 'gun'). The 'gun' was 'fired' by occluding the hole with the thumb. Gas was then ejected through the nozzle.

The tests were performed as follows: The child sat on the mother's or nurse's knee facing the tester; the tester sat on another chair just in front of the child holding the 'gun' in one hand and a watch in the other. He was in easy reach of the gas cylinder so that he could regulate the rate of flow. The 'gun' was presented to the child at 15-second intervals. That is to say the tester lifted it up and held it about 20 cm. in front of the child's face, on a level with his eyes. This presentation was performed gently and evenly so as not to startle the child.

The first three times the 'gun' was presented, although the gas was turned on it was not 'fired', i.e. no puff of gas was blown into the child's eye. During these preliminary presentations careful watch was kept on the child's reactions to see whether he blinked or grimaced spontaneously. At the fourth presentation the 'gun' was aimed at the child's eye as before, and after a moment it was 'fired'. The child's reaction was observed. It was usually of the same pattern on each subsequent occasion. Care was taken to distinguish between the eye blink due to the puff of air, and a spontaneous blink. With practice this was not difficult, as the eye blink due to the puff was usually associated with some screwing up of the eyes involving both the lower and upper lid. This had quite a different appearance from a spontaneous blink.

If the effect produced by the puff was insufficient, the gas flow was increased; if it was too violent the flow was decreased. The flow required had to be determined by trial and error in each individual case. An initial flow of 4 l./min. was found to be suitable, but sometimes the rate had to be increased progressively as the test continued.

Subsequent puffs were each made in the same way as the first. Great care was taken to allow a moment to elapse after the child had been presented with the 'gun' and had obviously noticed it, but before the 'gun' was fired. It was during this moment that it was possible to observe whether or not the child had been conditioned by the previous puff or puffs.

On the presentation at which it was thought that the child was conditioned, a puff was given in the same way as previously to reinforce the conditioning. At the next presentation no puff was given. If the child was really conditioned, he again blinked without a puff being given. If, however, a mistake had been made, a further puff was given after a few seconds delay and conditioning proceeded with. The number of puffs required before a child was conditioned was counted as his score. It was found that the proportion of children conditioning after 20 puffs was too few to make it worthwhile continuing the test for longer than this.

After the child was conditioned, deconditioning was performed by continuing to present the 'gun' at 15-second intervals as before, but without 'firing' it. The conditioned reflex often faded slowly, but the end point could be assessed with reasonable accuracy. Five presentations of the 'gun' were found to be all that was required for deconditioning. After this the results were unhelpful. If the end point of the test was not clear-cut the test was repeated after 20 minutes.

Results

In order to discover how normal children reacted to the test, it was performed on 168 children of apparently normal mentality between the ages of 5 months and 7 years. In 13 children the test had to be abandoned because of lack of co-operation or some other reason, leaving 155 children who are the subject of this part of the investigation. I performed a rough conventional developmental test first on each child to make sure that his intelligence corresponded with his chronological age. It is realized that the assessment of mental ability at this age is, at best, an inaccurate procedure, and some of the discrepancies in the results may be due to the fact that the child's intelligence was over or underestimated. Ideally the results of the puff test should be correlated with a formal intelligence test performed when the child is old enough. This investigation is proceeding.

The scattergram (Fig. 2) and Table 1 compiled from it give the results of the tests done on the 155 apparently normal children. Of the 12 children of 6 months and under, 11 could not be conditioned. This is the typical infantile response. Between the ages of 6½ and 12 months there were 49 children. Of these, 33 conditioned in less than 13 puffs, whereas 15 still gave the infantile type of reaction. One child conditioned in 16 puffs. Of the 32 children between 12½ and 18 months, all conditioned in 10 or less puffs, except for one child who required 19. Over the age of 18 months but under the age

TABLE 1
CORRELATION BETWEEN AGE AND EASE OF CONDITIONING IN 155 CHILDREN OF NORMAL INTELLIGENCE

Age	Apparently Normal Range		Better or Worse than Normal Range		Total No. of Children
	No. of Puffs	No. of Children	No. of Puffs	No. of Children	
<6 mths	20+	11	12	1	12
6½–12 mths	3–12	33	16–20+	16	49
12½–18 mths	2–10	31	19	1	32
18½ mths–4 yrs	2–6	45	7–13	2	47
>4 yrs	2	13	4–5	2	15

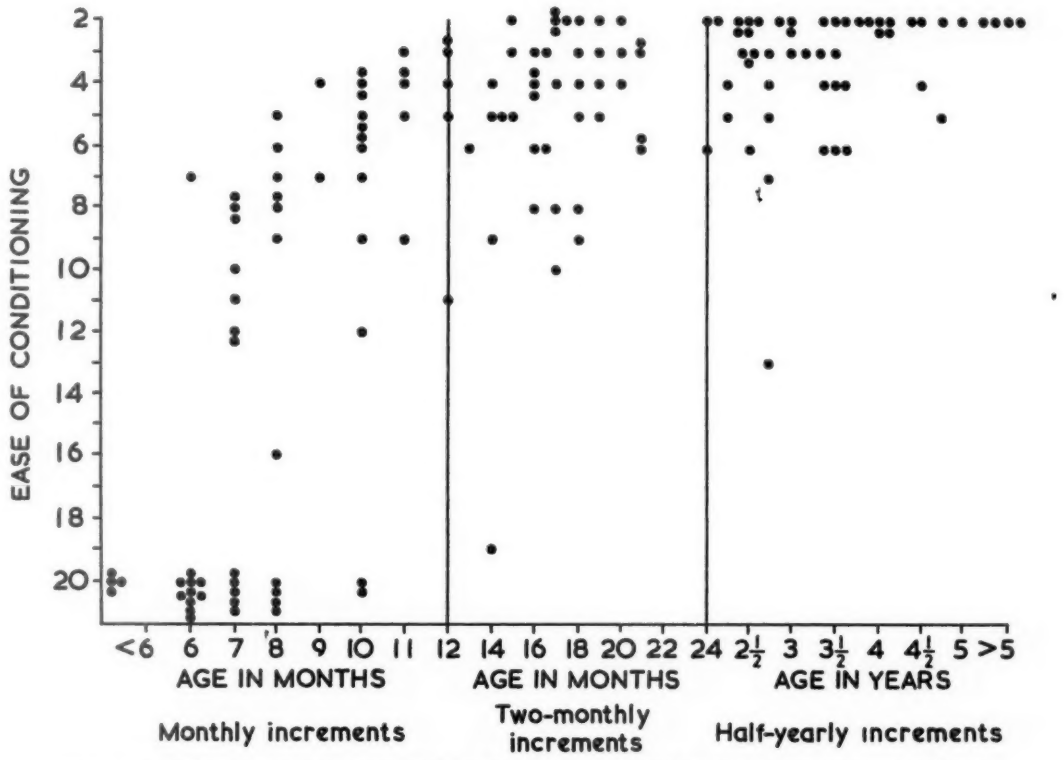

FIG. 2.—The puff test. Ease of conditioning compared with chronological age in 155 mentally normal children.

of 4 years, 45 children conditioned in between two and six puffs, but two required more. Of the 15 children over the age of 4 years, all but two conditioned in two puffs, which is the normal adult type of reaction.

In this experiment no child under the age of 14 months showed the typical adult type of reaction, and no child over 11 months showed the typical infantile type of reaction. From the point of view of the practical conduct of the test it will be seen that only two out of the 129 children who were successfully conditioned did so after 13 puffs.

So far I have successfully tested only 74 mentally defective children. Fig. 3 is a scattergram comparing ease of conditioning in mentally defective children with their chronological age. Fig. 4 shows ease of conditioning compared with approximate mental age. The former figure demonstrates the difficulty in conditioning these children, while the latter resembles the scattergram for normal children (Fig.).

Discussion

The puff test gave helpful results mainly between the ages of 6 months and 4 years. It so happens that this is an age group in which it is often difficult to assess intelligence.

The test only required a minimum of co-operation from the child and could be performed if the child looked at the 'gun' and did not cry or cover his eyes. No motor skill or educational knowledge was required, and the test could therefore be used in children with severe spasticity or deafness. Some athetoid children could not be tested owing to the difficulty in determining the end point. Another advantage of the test was that it was quick to perform; it never took longer than seven minutes and usually only two or three minutes.

I found no simple relationship between ease of deconditioning and age or intelligence. It did, however, give some indication of the fixity of the conditioning and for this reason it was of some value particularly in children who conditioned in two or three puffs.

Disadvantages and Difficulties. The test can only be performed on a child who can see and focus on the 'gun' and who has a normal corneal sensitivity. Most children laughed or smiled during the test, but a few cried or covered their eyes.

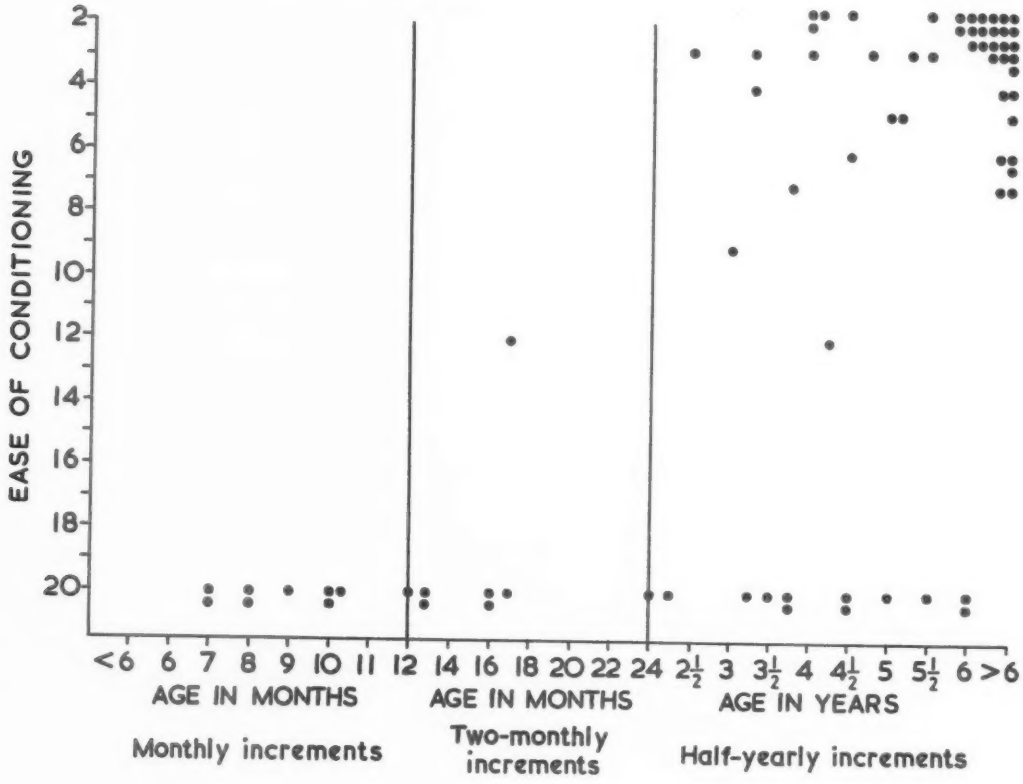

FIG. 3

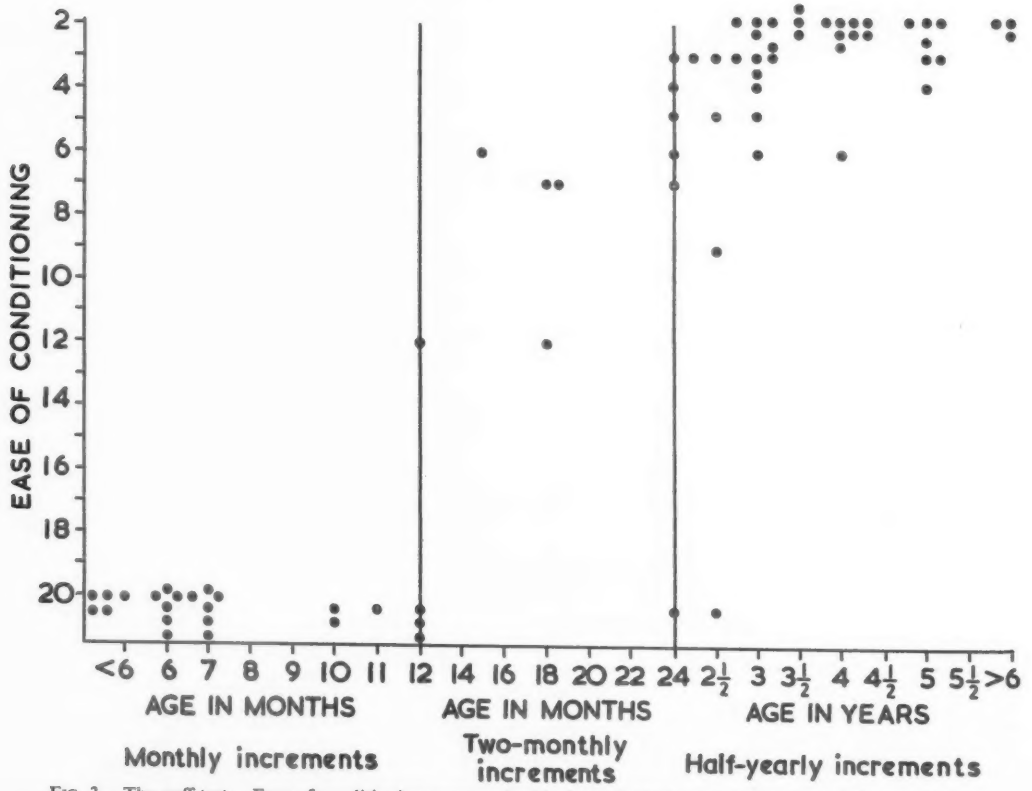

FIG. 4

FIG. 3.—The puff test. Ease of conditioning compared with chronological age in 74 mentally defective children.

FIG. 4.—The puff test. Ease of conditioning compared with approximate mental age in 74 mentally defective children.

Sometimes the end point was not clear-cut and the test had to be abandoned.

I found two abnormal reactions. The first was the 'stoic' reaction. After the first or second puff the child looked into the distance and appeared voluntarily to refuse to blink, even when the air flow was increased to 10 or more litres per minute. This reaction occurred four times in 155 normal, and once in 74 mentally retarded children over the age of 18 months.

The other special reaction I have termed the 'wait-for-it' reaction. This is very akin to what Pavlov called the 'what-is-it' or investigatory reflex (Pavlov, 1927, p. 12). The child obviously knew that he was about to have his face puffed, but took no avoiding action of any sort and seemed pleased when the puff came. Sometimes he opened his mouth as though expecting a spoon. On two occasions he blew back before the 'gun' was fired. The 'wait-for-it' reaction occurred five times in the normal children, but only in those under the age of 12 months. The 'wait-for-it' reaction occurred twice in mentally retarded children. One was a 4-year-old mongol with a mental age of from 12 to 18 months. She grizzled all the time the test was being performed until the twelfth puff. From then onward she stopped grizzling when the 'gun' was presented, laughed at the puff and then started grizzling again while waiting for the next puff. From the fifteenth puff onward she blew back at the puffer. She never blinked or screwed up her eyes. The other child was 5 years old, with a mental age of about 3 years. She showed a good conditioned eye blink at five, but from then on asked repeatedly when I was going to puff her face again. Two 10-year-old boys with low intelligence both opened their mouths as soon as the gun was presented. In each case the 'wait-for-it' reaction occurred in retarded children over the age of 4 years, whereas it only occurred in normal children under the age of 1 year. If the 'wait-for-it' reaction was well marked I took it as the conditioning end point, although it was not the expected conditioned reflex.

It is interesting to compare these results with those of Mateer (1918). She used Krasnogorski's (1913) method of allowing blindfolded children to hear a metronome and then giving them chocolate. By a mechanical method she recorded the movement of their throats as they swallowed saliva. She first tried the experiment on 50 unselected children, and estimated their intelligence afterwards. Her results are given in Table 2 and in graphic form in Fig. 5. She found a linear relationship between age and ease of conditioning for the ages of 1 to 5 years. Over that age the relationship broke down, perhaps because the older child, with his greater experience saw 'possibilities of variations in the procedure to which the younger child is oblivious'.

TABLE 2

EASE OF CONDITIONING COMPARED WITH CHRONOLOGICAL AGE IN 50 UNSELECTED CHILDREN*

No. of Cases	Age (yrs)	No. of Trials† (Average)	Range
5	1–2	8·0	7–9
7	2–3	6·7	6–8
6	3–4	5·3	3–8
12	4–5	3·8	3–5
8	5–6	4·1	3–5
9	6–7	5·0	3–7
3	7–8	4·3	4–5

* (After Mateer, 1918.)

† Three was the best result possible by Mateer's method and corresponds to the adult type of reaction.

The graph culled from Mateer's figures (Fig. 5) and the scattergram of the present experiment (Fig. 2) both show that there is a relationship between ease of conditioning and age. Mateer repeated the experiment on 12 mentally defective children. Her final conclusions were that ease of conditioning is 'not directly proportional to mental ability but is also relative to chronological age'; but she felt that she had devised a 'fundamental test of the mental process'.

A very similar experiment to the one which I performed has also been described by Morgan and Morgan (1944). They puffed air into the eyes of babies and obtained a wink. At the next presentation five seconds later, they watched to see whether the baby would wink in anticipation of the puff or not. In either event a further puff was given. If the child did not learn the lesson assigned in the experiment by 100 presentations he was considered to have failed. Forty-two infants were treated; all children over the age of 65 days passed the test with one exception; all children under the age of 54 days failed the test; some passed and some failed between 54 and 65 days. The child over the age of 65 days who failed was 4 months old. At the age of 5 months a Cattel test was performed, and her I.Q. was recorded as being 76. The authors state that to perform the test successfully a child must be old enough, and must be able to see. They also thought that if an infant over 65 days old failed to pass the test it might be due to inferior intelligence, but that they had insufficient evidence to verify or repudiate this hypothesis.

Conclusion

We can now consider the three questions which these experiments are designed to answer.

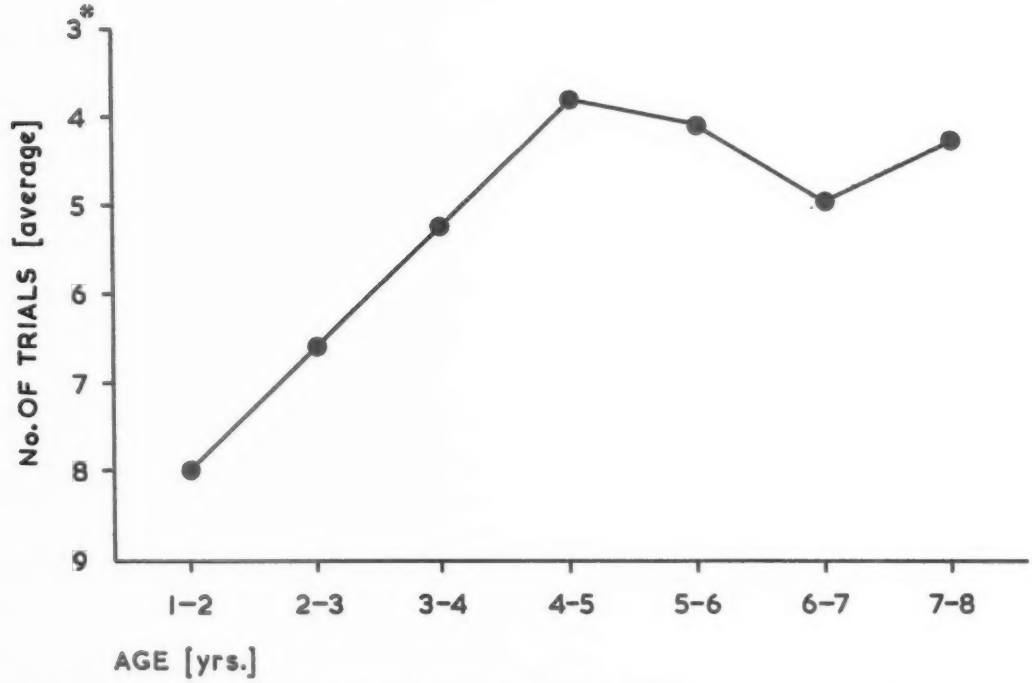

FIG. 5.—Ease of conditioning compared with chronological age in 50 unselected children. Graphic representation of Table 2 (from Mateer 1918); three was the best possible result by Mateer's method.

Mateer's experiments and mine, although using different techniques, both showed an almost linear relationship between ease of conditioning and age in mentally normal children up to about 5 years of age. Above this age the power of reasoning obscured the straightforward conditioned reflex response. The 'adult type' of reaction described above only occurred with adults who had not been told previously what to expect. I performed a small series of experiments on sophisticated medical students who had heard about the test, although they had not seen it in action. The results obtained were quite bizarre.

The experiments showed a relationship between ease of conditioning and *mental* age in mentally retarded children, although there was a much wider scatter in the results with mentally retarded than with normal children. This was probably due in part to the difficulty in measuring mental age with accuracy.

There is a formidable battery of developmental tests which can be used to measure the mental age of young children. Unfortunately most of these tests require either manipulative skill, such as walking or building a tower of bricks, or knowledge, which has to be learnt from others, such as the recognition of a picture or obedience to a command. The puff test has the advantage that neither of these skills are required. It is therefore of particular value in testing the mental ability of children with some physical handicap such as spasticity or deafness. The following case reports illustrate this.

Case 1. This child, 2 years and 5 months old, had a mild right hemiplegia and was thought to be mentally defective. In the puff test she conditioned easily in two puffs, which is the adult-type of reaction and this made it improbable that she was grossly mentally defective; in fact, she was found to be completely deaf. Normal developmental testing had been virtually impossible owing to the dual disability.

Case 2. This boy of 8 months had mild kernikterus in the neonatal period due to Rhesus incompatibility. He was seen to smile at 4 weeks and at 6 weeks his motor development was described as 'better than average'. By 5 months, however, his motor development was very poor and he was regarded as being mentally retarded. There were no athetoid movements at that time. At 8 months he could not sit, had the head control of a 4-month-old baby, and did not vocalize. A puff test, however, gave a 'wait-for-it' reaction from 10 puffs onward. With each puff the boy gave a deep breath as many babies do, and from 13 puffs onward, gave a conditioned deep breath *before* each puff. (He is the only child in whom I have observed this.)

If 13 is taken as the end point, it is most unlikely that this baby is severely mentally retarded. This is confirmed by his early developmental history, and the fact that he has since been shown to be deaf and to be developing athetosis with hypotonia.

By using a tactile or auditory unconditioned stimulus the puff test could be modified for use in blind children.

The test must obviously be used in conjunction with other well-recognized tests of intelligence. In some cases the end point is too indefinite to be of any value. This is particularly so if the test is performed in distracting surroundings. The information it gives is limited, but the test is easy to perform, takes a short time, can be repeated if necessary, and occasionally gives information unobtainable in any other way. It is obvious that a great deal of further study is required, but it does seem that the test may prove to be of value either in itself, or as a basis for other tests.

Summary

A conditioned reflex has been established in a number of children under standard conditions. The reflex used was the eye blink when air was puffed into the child's eye.

The test was performed on 155 mentally normal children with the following results: Children of 6 months old and under could not be conditioned; over the age of 6 months conditioning became progressively easier until the typical adult response of immediate conditioning was reached at about 4 years of age.

Provisional results in 74 mentally defective children are also reported. As a group they were more difficult to condition than ordinary children of the same chronologial age. When speed of conditioning in the mentally defective children was correlated with their mental age, the ease of conditioning approximated to that of normal children, although there was a wider scatter.

It is suggested that the puff test can be used as a simple intelligence test. It has the following advantages: It is quick to perform, needs little apparatus, and only requires a minimum of co-operation from the child, and in addition requires no motor skill nor educational knowledge on the part of the child.

Two unusual reactions were noticed. In the 'stoic' reaction the child voluntarily refused to blink. This reaction occurred in children over the age of 18 months. In the 'wait-for-it' reaction which occurred in normal children under 12 months old, the child gave evidence that he knew that he was about to be puffed, but took no avoiding action. If well marked, this was taken as the end point of conditioning.

The puff test has been found to be of value in assessing the intelligence of young children with physical handicaps such as spasticity or deafness. Like any other intelligence test, it cannot be used alone, but in conjunction with other tests it should prove valuable.

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A SURVEY OF A GROUP OF CHILDREN WITH MENTAL AND PHYSICAL HANDICAPS TREATED IN AN ORTHOPAEDIC HOSPITAL

BY

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In the recent correspondence in the *Lancet* (Capon, Kirman and Todd, 1959; Quibell, Stephen and Whatley, 1959) and in the non-medical press, great interest has been shown in the treatment of children with mental and physical handicaps. These children represent a hardcore problem, on the borderland between several branches of medicine. It is unfortunate, in our opinion, that in England and Wales the severely mentally handicapped children are not the concern of the education authorities, as is the case in Scotland where they have responsibility for the occupation centres (Younghusband Report on Social Workers, 1959). In the mental deficiency institutions there are some mentally handicapped children with associated physical handicaps; in the children's hospitals there are physically handicapped children with associated mental handicaps. Two of the main groups are children suffering from cerebral palsy and children with spina bifida, associated with myelomeningocele and hydrocephalus. At present, it seems that the placement of these children depends, not on the degree or nature of the physical disability, but on the degree of mental retardation. It may be that the physical handicaps in this borderland group of children tend to be the same, whether they are treated in mental deficiency institutions or in children's hospitals.

We were unable to find conclusive figures of the incidence of spina bifida children with associated mental defect; however, there are figures which suggest that there are quite a number. Hilliard and Kirman (1957) state that of 54 in-patients at the Fountain Hospital with hydrocephalus, 11 had spina bifida. Nash (1957) in his Hunterian Lecture, estimated that there had been an increase of about 500 children a year surviving with congenital spinal palsy since 1954, which in the 10-year period reviewed represents a total of some 5,000 severely paraplegic children. Nash gave no indication of the range of intelligence of these children, but it seems legitimate to assume that the number of educationally sub-normal or ineducable children with spina bifida is increasing.

The incidence of cerebral palsy among children of school age is one to two per 1,000, and we know that approximately 40% of children with cerebral palsy have I.Q.s below 70. Hilliard and Kirman (1957) gave the number of cerebral palsied children at the Fountain Hospital in 1955 as 228 out of a total of 777.

Present Inquiry

In the recent correspondence in the *Lancet*, at least two writers were successfully treating children with mental and physical handicaps in a general Children's Hospital. No one in this country appears to have reported the results achieved. Wallin (1949) quoted two American studies of the treatment of mental defectives with cerebral palsy, from which it appeared that some mental defectives showed marked improvement in daily living functions after treatment.

An attempt has been made in this paper to evaluate the response to treatment of 40 physically and mentally handicapped children at Chailey Heritage.

Forty educationally sub-normal and ? ineducable children, none of whom had been at Chailey for less than one year were included in the sample; 33 were fairly certainly educationally sub-normal, seven were doubtfully educable. Their ages ranged from 2 to 16 years.

There was one case of poliomyelitis, one case of toxoplasmosis, one case of phenylketonuria with poliomyelitis, 30 cases of cerebral palsy and seven cases of spina bifida. (This is an over-simplification of diagnoses, but it does show that the largest groups were the cases of cerebral palsy and of spina bifida.)

There were the following associated or additional

handicaps: 36 out of 40 had one or more associated handicaps: 14 had one, 13 had two, eight had three. The range of handicaps was as follows: vision, hearing, speech, epilepsy, and urological conditions (Tables 1 and 2). Fourteen of this group were rated as having an associated somatic hazard: this is a particular physical hazard to which a child is subject because of the main handicap. For example, a spina bifida case is liable to develop pathological fractures or trophic ulcers which may require hospital treatment, sometimes for a long period.

No control groups were used, but as the purpose was to show the progress made by these children in an orthopaedic children's hospital, this is not a major objection. It is possible that more intelligent children might make more and/or quicker progress, and that some of these children will make more progress as methods of treatment change.

The children were assessed in four ways:

(1) An attempt was made to rate the improvement in daily living functions in each child over a period of time. As this was a retrograde study, it turned out to be impossible to rate the children over corresponding periods of time, and we have times for progress made in ambulation only.

(2) An assessment of the present emotional adjustment of a sub-sample was made by one of us (E.W.).

(3) Present educational attainments were supplied by the headmaster.

(4) Data on home conditions were given by the almoner.

Daily Living Function

The concept of assessing the progress of children in terms of daily living function derives from earlier work at Chailey (Quibell, 1956). This work is an adaptation of the Bellevue scale used in the rehabilitation of adults, and covers all activities essential for daily living. This scale was too detailed for the purpose of a group study, although it is invaluable for the assessment of the individual child; however, the scale used here is based on this work. The areas to be assessed were divided into: (1) Speech; (2) ambulation; (3) washing and dressing; (4) feeding; (5) toilet management; (6) fine hand activities.

Two assessments were made of each child; the first was obtained from staff who remembered the child and/or the case notes; the second was made with the help of the staff who are now treating the child. The assessments of the younger children were made with the help of an *ad hoc* developmental scale in order to allow for age.

The method of scoring was a three-point scale, 0-1-2 in each area, with a minus sign if a child was admitted with no difficulty in the particular area; e.g. if a child came in able to walk he got a — in the ambulatory column. 0 indicated total dependence; 1, partial independence; 2, independence. The improvement score was arrived at by subtracting the initial score from the final score. These classes are too broad; more classes, more clearly defined are needed. However, points of improvement do represent worthwhile gains in an essential function; worthwhile for the child in terms of independence and morale, and ultimately worthwhile from the economic point of view because such patients then require less nursing care.

The total of 40 children were divided into four groups according to degree of functional independence.

Group I: Children now functionally independent for daily living.

Group II: Children sufficiently independent for placement on the ambulant side but not entirely independent.

Group III: Children requiring ward placement, but showing improvement.

TABLE 1
NUMBER OF ASSOCIATED HANDICAPS IN GROUPS I-IV

Group	No.	Handicaps			
		None	One	Two	Three
I	11	1	5	2	3
II	10	0	2	4	4
III	13	3	6	3	1
IV	6	0	1	4	1

TABLE 2
INCIDENCE OF HANDICAPS

roup	No.	Handicaps					
		Vision	Hearing	Speech	Epilepsy	Genito-urinary	Total
I	11	6	1	4	3	1	15
II	10	6	3	7	3	3	22
III	13	4	0	4	3	4	15
IV	6	3	1	6	1	1	12

TABLE 3
I.Q. RANGE

Group	No.	I.Q. Range			
		61-70	51-60	41-50	Untestable
I	11	6	5	—	—
II	10	7	3	—	—
III	13	6	2	3	2
IV	6	2	1	0	3

Group IV: Children requiring ward placement but considered to be making no worthwhile progress.

Group I. This group consisted of 11 children between the ages of 8 and 15, functionally independent for daily living. They were all on the ambulant side and all were in the educationally sub-normal intelligence range (Table 3). Of these 11 children, four had, on the functional scale, maintained their status since admission. This is an indication of the limitations of this scale, i.e. the ceiling is too low; these four children are having treatment to improve their speed and co-ordination in functions in which they were independent on admission. The other seven children have all achieved worthwhile improvement in daily living functions, and four were promoted from the ward side because of such improvement.

Four children in this group were unable to walk on admission and are now fully ambulant. This means that they can walk 100 yards, go up and down gradients, turn, and climb steps or stairs with or without appliances. In fact nine children in this group have no orthopaedic appliances now.

One further comment on this group; we made a general prediction on the future placement of the entire group of 40, and only one child in this group was judged likely to make open employment. This may be gross underestimation, but even if it is, it does suggest that for many of these children the final goal at present is a basic level in educational skills and as much functional independence as possible. There still remains consideration of the next step when they leave school, e.g. placement in centres for young adult spastics.

Group II. This group consisted of 10 children between the ages of 9 and 16 sufficiently independent for placement on the ambulant side but not entirely independent. These children were all within the educationally sub-normal intelligence range.

All the children in this group have shown some improvement in daily living functions on our criteria, and six were promoted from the ward because of improvement.

Five children were unable to walk on admission and are now fully ambulant.

On the educational side, no child in this group is totally unable to read.

Group III. This group consisted of 13 children between the ages of 2 and 14 requiring ward placement, but showing improvement.

Eleven were treated and only one was able to walk on admission. Of the 11 treated, four are now walking slowly and are making progress, six can walk a few steps with crutches or walkers, but their future progress is considered doubtful; however, to be able to walk a few steps may make the difference between being totally dependent or independent for toilet, one of the most frequent and continuing functions of daily life.

Those under 7 years of age in this group made it of special interest because they included the — ? ineducable children; as Chailey is a school as well as a hospital, the older children are almost by definition *not* ineducable. It is a small sample, but possibly one can argue that extreme cases can be used as illustrations with some validity. Of these seven children, two were awaiting transfer as ineducable, and two or three others may prove to be ineducable. Five were in the nursery class, and two were on the babies' ward. The teacher's comments on the five in the nursery class were that five improved in speech, four in contacts with other children, and four made some use of nursery apparatus; they fitted into the nursery group reasonably well with younger normal children of their own mental age level. The Sister on the babies' ward said that the two children in her ward seemed reasonably happy.

On the daily living functions improvement chart the assessments were made with the help of the *ad hoc* developmental scale: in speech, five out of seven showed some improvement.

All were unable to walk on admission; two are now walking alone and are making progress to full ambulation; three are now able to walk a few steps with crutches or walkers; and two are still unable to walk. The stages of ambulation were supplied by the physiotherapists.

Four have made some progress in washing and dressing.

Three were feeding themselves and one 3-year-old phenylketonuric with poliomyelitis affecting the legs was beginning to feed himself.

Three had progressed in toilet training to being clean and dry, i.e. they indicated their toilet needs although they were not, of course, independent.

With regard to fine hand activities, two appeared normal for their mental age; two had made some

progress; and two, whose hands were affected, because they are quadriplegics, showed no change.

On their social background, three were illegitimate, and two of these who were separated before the age of 3 years remained at Chailey during the holidays, and had no regular visitors; both seemed fairly well adjusted, though it was difficult to assess this, and they were making progress.

These 7 ineducable children are the hardcore, and if one can show improvement in these children it seems reasonable to suppose that one can generalize from this to some extent. Our results show that they can improve. They seem to be reasonably adjusted and making some progress in the nursery class, so the possibility is that young mentally and physically handicapped children can be treated in nursery classes with physically handicapped but younger children of their own mental age level. In babies' wards the mental age seems less relevant. We expect that older imbecile children, i.e. from 7 or 8 years, would require a special sub-unit within the hospital (Quibell *et al.*, 1959).

Group IV. This group consisted of six children between the ages of 6 and 15 who were considered to be making no worthwhile progress.

Of these six children, three were within the educationally sub-normal range, three were untestable, and of these, two were almost certainly grossly defective. In the three educationally subnormal children the total physical handicap seemed so gross that physical progress was almost impossible. The two gross defectives were also grossly physically handicapped.

This group is too small to justify conclusions, but it is interesting that half of them are, as far as one can tell, educationally sub-normal (i.e. not ineducable on intelligence tests).

Details for the four groups are set out in Tables 4 to 9.

TABLE 4
NUMBER OF TREATMENTS IN EACH GROUP

Group	No.	No. of Treatments							
		Seven	Six	Five	Four	Three	Two	One	Nil
I	11	—	—	—	1	5	5	—	
II	10	—	2	1	3	2	2	—	
III	13	—	—	5	2	1	6	—	1
IV	6	1	—	2	2	1	—	—	

TABLE 5
NUMBER AND NATURE OF TREATMENTS GIVEN IN EACH GROUP

Group	No.	Treatment						
		Physiotherapy + R.G.	Occupational Therapy	Speech Therapy	Drugs	Surgery	Plaster	Remedial Teaching
I	11	10	6	4	4	1	4	0
II	10	9	8	4	6	6	4	2
III	13	12	6	3	4	5	6	2
IV	6	6	5	6	5	1	2	3

TABLE 6
NUMBERS AND TYPES OF APPLIANCES USED IN EACH GROUP

Group	No.	Appliances			
		Orthopaedic	Protective Cup and Urinal Bags	Sensory*	Total
I	11	2	0	5	7
II	10	9	4	3	16
III	13	20	2	4	26
IV	6	7	0	2	9

* D[illegible]-aids, glasses.

TABLE 7
DEGREES OF IMPROVEMENT REGISTERED IN EACH GROUP

Group	No. Treated	Degrees of Improvement									
		7 (No.)	6 (No.)	5 (No.)	4 (No.)	3 (No.)	2 (No.)	1 (No.)	0 (No.)	Maintained (No.)	Promoted from Ward to School (No.)
I	7	1	1	—	—	3	1	1	—	4	4
II	10	1	1	—	4	3	1	0	0	—	6
III	13	—	—	2	5	3	2	1	—	—	0
IV	6	—	—	—	—	1	—	—	5	—	0

TABLE 8
SHOWING CHANGE AFTER SPEECH THERAPY TREATMENT

Group	No. Treated	Improvement			
		Much Improved	Improved	No Change	Deteriorated
I	4	2	1	—	1
II	4	1	3	—	—
III	3	1	2	—	—
IV	6	—	—	6	—

Assessment of the Emotional Adjustment of a Sub-sample. Seventeen boys were assessed by one of us on present adjustment, using the Maudsley descriptive code (Cameron, 1955) as an adjunct, particularly where the children had not been seen recently. The sub-sample consisted of 13 ambulant boys who were educationally sub-normal and between the ages of 8 and 16, and four more severely handicapped educationally sub-normal boys from the wards over the age of 12. These boys were rated on a three-point scale as: adjusted, mildly maladjusted and severely maladjusted.

Three were found to be adjusted, 12 mildly maladjusted and two grossly maladjusted.

This is a very small sample, and it would be useful to assess the whole group in this way. The amount of mild maladjustment seems high, but possibly not for a dull physically handicapped population. Dunsdon (1952) found, using teachers' ratings, that of 16 cerebral palsied children with I.Q.s below 70, only two were reasonably stable.

The data for the Maudsley descriptive code were collected by the psychiatrist and psychologist, from the warden, the assistant matron and one staff nurse. It seems worth mentioning that in the opinion of all of us there may be a need for a special unit for these older mentally handicapped (educationally sub-normal) children, where they could have a fairly simple routine and occupations geared to their intellectual limitations, and not have to compete with, or hold back those of average and above-average intelligence. It may be impossible to make these doubly handicapped children completely adjusted, but it would be interesting to have an experimental unit in order to see how much one could achieve. These are all educationally sub-

TABLE 9
PHYSIOTHERAPY AND MOBILIZATION

Group	Ambulatory Stage	Nos.
I	Unable to walk on admission, now fully ambulant	4
	Time to attain ambulation: One year	2
	Three years ..	1
	Five years	1
	Co-ordination, number treated	6
	Able to walk on admission	7
II	Unable to walk on admission, now fully ambulant	5
	Time to attain ambulation: Two years	1
	Four years ..	1
	Five years	1
	Six years	2
III	Unable to walk on admission	11
	Of these	
	a. Now walking slowly, should make progress	4
	After five months' treatment	1
	After one year's treatment	2
	After five years' treatment	1
	b. Now walking a few steps with crutches or walker. Further progress doubtful ..	6
	After six months' treatment	1
	After two years' treatment	2
	After three years' treatment	2
	After four years' treatment	1
	c. Still unable to walk after two years' treatment	1
IV	Unable to walk on admission	6
	Still unable to walk	6

normal children, so they are catered for on the educational side in small classes.

Sixteen out of these 17 children have some degree of brain damage and were rated as 'immature' on the Maudsley descriptive code; six out of 17 were described as having 'tendency to outgoing aggressive behaviour', eight as having 'tendency to passive withdrawn behaviour'. This is too small a sample from which to draw conclusions, but it is worth noting that the incidence of aggressive and withdrawn behaviour is approximately equal in this group of brain-damaged children.

Present Educational Status

The 29 educationally sub-normal children in this group had a chronological age range from 8 to 16 years. The reading ages on test ranged from 11 years to under 5 years, with a mean of 7 years (excluding two non-readers). Arithmetic ages on test ranged from 9 years to under 5 years, with a mean of 7 years (excluding one child under 5 who had made no beginning in formal number work). Out of 10 children of 8 years or over with a reading age of under 6 six had speech defects (with or without hearing loss), two had missed much schooling, and two were epileptic. However, of six children of 8 years or over with a reading age of 8+ (only one had no associated handicap) four had visual defects, four had speech defects, and two had epilepsy. For example, a girl of 10 with a speech defect, a visual defect and pathological temper tantrums, had a reading age of 8 years. Again, arguing from extreme cases, it does seem that some children with the most extraordinary assortment of adverse factors do learn to read.

Home Conditions

It can be seen from Table 10 that the social factors for the whole group vary considerably. Only very tentative inferences can be made from such a small group, but the following points can, we think, be considered.

There seems no evidence from our figures of a relation between adverse social factors and failure to make progress. The home circumstances of the six children in Group IV, varied from good homes to broken homes with every conceivable adverse factor but actually all these children were either visited by relatives, or went home for part of the holidays, or both. Conversely, four children of the 40 surveyed had no visitors, and remained at Chailey during the holidays. Of these, three were in Group III (1, 2, and 4 degrees of improvement) and one was in Group II (5 degrees of improvement).

TABLE 10

HOME CIRCUMSTANCES OF TOTAL GROUP OF 40 CHILDREN

Condition	No. of Children
Illegitimate	6
Both parents mentally and physically well	24
Visited	33
Not visited	7
Home for holidays	32
Placements other than home before admission:	
Five	1
Four	5
Three	6
Two	14
One	14
Separated before the age of 3	17

One would expect that had these four children also had good home support, they would have made better progress.

Many of the children with adverse social factors, such as broken homes, early separation from their families, and long and sometimes eventful hospitalization, exhibited only minor degrees of maladjustment, and did show improvement. We suggest that this may be related to the policy (not so rare in many long-stay paediatric hospitals) of meeting their needs on the spot as far as possible, including warm personal relations with individual members of staff, a generally stimulating daily programme, and of maintaining active links with their families through the almoner's department, as much as distance and the overall position of the families allow.

Operations

In addition to the operations outlined in Table 11 orthopaedic surgery may include other operations to correct deformities in spina bifida cases or to treat pathological fractures.

Neurosurgery may involve excision of a myelomeningocele, drainage of a chronic subdural haematoma, or insertion of a Spitz-Holter valve into the ventricular system in cases of spina bifida with increasing hydrocephalus.

In plastic surgery, trophic ulcers or resultant adherent scars in cases of spina bifida with paraplegia, may call for excision or grafting; palatopharyngeal mobilization and closure may improve speech function and swallowing in cerebral palsy.

Discussion

These results show that some children with severe mental and physical handicaps do make demonstrable gains in functional independence after treatment in a long-stay children's hospital. The two main groups considered in this study are the mentally handicapped children with (*a*) cerebral palsy and

TABLE 11
OPERATIONS ON 13 CHILDREN

Orthopaedic	No.	Urological	No.	Plastic	No.	Miscellaneous	No.
Eggars for over-active hamstrings	3	Bladder neck resection	1	Submandibular gland excision	1	Bilateral orchidoplexy	1
Grice grafts (stabilization of foot)	2	Urethral plication	1			Minor operation	1
Amputation terminal phalanges big toes	1	Suprapubic cystotomy	1			Tonsillectomy	1
Tarsal arthrodesis	1	Ileocutaneous ureterostomy	1				
Tendon transfer	1						
Flexor or adductor tenotomies	3						
Total	11		4		1		3

(*b*) spina bifida with associated myelomeningocele. It appears that the minimum I.Q. or mental age necessary in order to make useful progress in daily living function is much lower than may have been assumed. Our survey suggests that the children who did not show improvement, could not, because of the severity of the physical handicap, rather than because of their mental dullness. In other words imbeciles may make some response, idiots probably not. Physically and mentally handicapped children require not only medical treatment and special education, but a wide range of training in daily life functions: this study indicates that they can respond to such a programme.

All the evidence suggests that the number of these children who survive is increasing, and therefore knowledge of and planning for their needs are urgent.

In our opinion an essential feature of this kind of work involving as it does, so many forms of treatment, is that there should be one person responsible for the over-all direction and planning of treatment for every child, as recommended in the Piercy Committee report. In this study the medico-social side of the work was co-ordinated and planned by a paediatrician.

Wall (Director, National Foundation for Educational Research) wrote in *The Times Educational Supplement*, October 30, 1959: 'If it did not happen daily, it would seem incredible that decisions involving hundreds of thousands of children and many more thousands of pounds are taken with the object of achieving certain ends, and nobody attempts any kind of evaluation of the results more objective than the opinions of those who take the decisions.' We submit, that with the comparatively small and clearly defined group of the mentally and physically handicapped, an enquiry into this matter could be undertaken now. Ours is a crude and retrospective survey, but a more refined, prospective assessment on these or similar lines would in our opinion not be difficult to devise and carry out.

Conclusion

Of 36 children, 31 showed improvement in the daily living functions, including speech (four of the group of 40 were excluded because they were independent for these functions on admission).

The improvement in ambulation has been analysed as follows: of 26 children unable to walk on admission, nine are now fully ambulant, four are now walking slowly and expected to make progress, six are walking a few steps, while seven are still unable to walk. Nineteen out of 26 children have therefore made worthwhile progress in ambulation.

We are grateful to the many members of the staff at Chailey who co-operated in this survey.

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OBSERVATIONS ON THE CLINICAL COURSE AND TREATMENT OF ONE HUNDRED CASES OF STILL'S DISEASE

BY

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Just over 60 years have elapsed since Still's (1897) classical description of rheumatoid disease in children, yet, despite extensive study, the pathogenesis remains obscure. To include it in a composite group of 'collagen' disorders may ultimately help to solve the problem of aetiology, as certain of the histological changes are common to them all. On the other hand there are many discrepancies. Those, for instance, who point to a close affinity between rheumatic and rheumatoid disease in childhood find it difficult to ascribe the latter to an allergic process involving a streptococcal infection. Then there is the extraordinary decline in the incidence of acute rheumatism in this country over the past 50 years (Cox and Schlesinger, 1956), which has by no means been reflected in our experience in the case of Still's disease.

The only apparent advance has been in treatment; steroid therapy has a dramatic effect in both these diseases, as it has to a lesser extent in other 'collagen' disorders. Some believe that any improvement is merely temporary, and the view has been put forward that results in the treatment of these diseases are as good with high doses of aspirin as with cortisone (Medical Research Council and American Heart Association Joint Report, 1955; Joint Committee Reports of the Medical Research Council and Nuffield Foundation, 1954, 1955, 1957a; Ansell, Bywaters and Isdale, 1956).

An assessment of the long-term effect of steroids in rheumatoid arthritis in children has been one of the main purposes of this investigation and our conclusions differ from those of Ansell *et al.* (1956). One hundred cases have been followed for up to 15 years at The Hospital for Sick Children, Great Ormond Street, and at University College Hospital, London, and recent personal examination, or in a very few instances reports from their local doctors, have brought their progress up to date. The account which follows is divided into two parts. One deals with the course and complications observed in the series as a whole, in the hope that something further may be learned of the natural history of the disease. The other gives the findings in the 63 children who received steroids, showing the immediate and eventual results of treatment.

PART I: CLINICAL

Course and Complications

Age at Onset. Still's disease is well known to occur earlier than acute rheumatism. In the group we are considering of 60 girls and 40 boys the most frequent age of onset was well below 5 years, and the incidence of first attacks declined sharply in the second decade (Fig. 1).

Mode of Onset. Still's disease compared with rheumatoid arthritis in adults generally runs a much more acute course, quite often affecting many parts of the body before settling in the joints. The main features in these circumstances may be high fever, rash, lymphadenopathy and leucocytosis, with only an occasional ache in the limbs. Such children may, therefore, suffer many investigations to exclude other diseases, and a variety of antibiotics are often given in vain. It is generally at this early stage that obvious or insidious pericarditis and pneumonitis can occur. Eighteen children in the series behaved in this manner. The average interval between systemic and arthritic involvement in this group was four months. In one patient the interval was much longer, three years, and in another there were four separate bouts of fever before the nature of the disease became clear.

Fever. If the disease is left to run its natural course, pyrexia may persist for a long time, even for years. The fever may also assume a peculiar

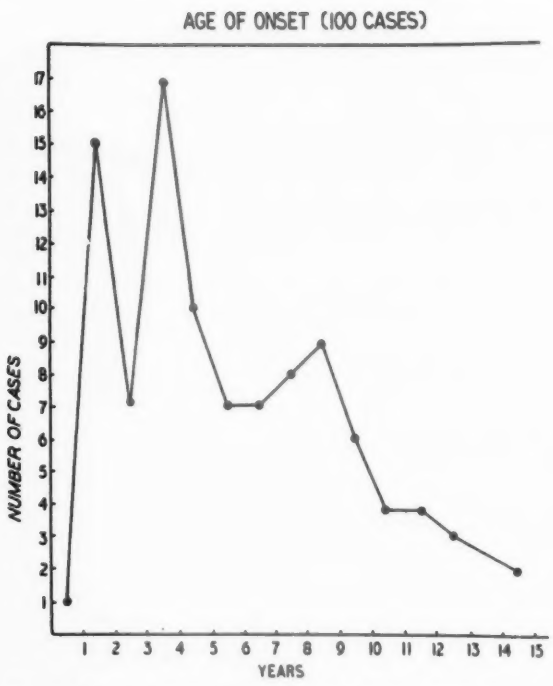

FIG. 1.—Age at onset of symptoms in 100 cases of Still's disease.

periodicity, but the temperature chart shows greater irregularity than in Hodgkin's disease and brucellosis (Schlesinger, 1949). Sometimes the fever is very high, the child feels extremely ill, vomiting is frequent and the condition becomes serious. It is under such circumstances that steroids are particularly effective, but the dose may have to be large and the course of treatment prolonged to keep the fever and other symptoms under control.

Rash. A rash occurred in about 40% of patients. It is a feature which helps in the diagnosis of an obscure case. Only rarely is it present without an associated lymphadenopathy and leucocytosis. It resembles erythema annulare of acute rheumatism in its wide distribution and in the way it comes and goes, unaffected by any form of treatment (Fig. 2). It may be a sign of an extensive systemic rheumatoid disorder and yet does not necessarily carry a gloomy prognosis.

A rash was the main presenting sign in five cases, with varying degrees of fever and lymphadenopathy. Joint involvement was limited to a transient arthralgia with little or no swelling. These children have been followed for four to six years. None have developed arthritis; three are now quite well, but two have a persistent rash and slight malaise.

Skin biopsy of the rash demonstrated coarse oedematous collagen fibres with abnormal staining properties and perivascular cellular infiltration in the upper portion of the corium, with polymorphs and, to a lesser extent, lymphocytes, plasma cells and histiocytes predominating (Fig. 3). Sometimes the rash is appreciably elevated and has an urticarial quality, and rarely it is purpuric, when patches of skin show purple striae or even gangrenous lesions, leaving beneath a healthy healing area (Figs. 4 and 5).

Leucocytosis. A leucocytosis of up to 30,000/c.mm. with 80 to 90% neutrophil polymorphs, is a well-known phenomenon, chiefly encountered at a florid stage of the disease. It occurred in 44% in our series. This reaction was investigated by Schlesinger and Cathie (1951), and a marked increase of granulocyte cells was discovered in the bone marrow, with a shift to the left. This leucocytic reaction may easily lead to an erroneous diagnosis of osteomyelitis, or of suppurative arthritis, when a single joint only is at first involved.

Occasionally in severe cases the bone marrow seems to become exhausted by continuous stimulation and a profound pancytopenia develops.

Effect of Trauma. In an appreciable number, 14 in the present series, arthritis began in the very joint which had suffered a minor injury shortly before. Selye might interpret this as a *locus minoris resistentiae*, reacting to generalized systemic stress otherwise insufficient to affect healthy tissues. It might equally well be the result of some local circulatory damage, such as is thought to precipitate bone tuberculosis or osteomyelitis in similar circumstances.

Lymphadenopathy. This is a sign of systemic rather than of arthritic involvement and bears no regional relationship to the joints involved. The glands can be greatly enlarged in the absence of arthritis, and gross arthritis may proceed eventually to crippling without lymphadenopathy at any stage. The epitrochlear and axillary glands are the most likely to become easily palpable. Biopsy has not revealed more than reactive hyperplasia. Eventually with remission of the disease the glands resume their normal size. Splenomegaly occurs less frequently.

Arthritis. The type of joint involvement in Still's disease is so well known that further description would be superfluous. Possible delay in the appearance of arthritis in the course of the disease has already been sufficiently emphasized. Quite often a fleeting arthralgia or transient periarticular swelling precedes the onset of more chronic poly-

FIG. 2.—Rheumatoid rash in a girl of 7 years with other signs of systemic involvement.

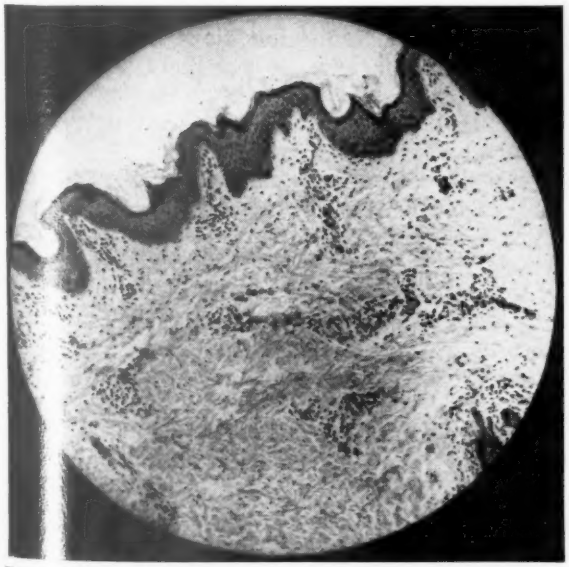

FIG. —Histological picture of a skin biopsy in the region of a rheumatoid rash. (× 58.)

FIG. 4.—Purple striae above the knee in a girl aged 10 years with severe rheumatoid disease.

FIG. 5.—Gangrenous skin lesion over the nose in the same child (*c.f.* Fig. 4), which finally healed completely.

arthritis. This does not mean that joint lesions cannot be the predominant feature from the very beginning. The disease in children often takes the adult form, but even then there may be an unusual course. The spine is frequently affected, particularly in the cervical region, and neck stiffness is commonly an early manifestation. When this is part of a generalized arthritis the interpretation is clear but if, as in three of our children, the trouble is at first confined to the neck, causing severe torticollis, the diagnosis may present difficulty.

It is helpful to divide arthritis into 'wet' and 'dry' types, depending on the amount of inflammatory exudate. With large effusions the joint cartilage is offered some protection, and there is much less pain and hardly any protective spasm. In our experience the chance of eventual complete healing is then far greater, provided the capsule has not been so widely stretched as to allow subluxation to occur. The outlook in the 'dry' variety is not so good, for the joint surfaces easily become eroded, adhesions form and muscle spasm ends in contractures. Although finally the disease may burn itself out, the child may be left a complete cripple with ankylosis or superimposed osteo-arthritis.

The sudden appearance of *monarticular arthritis* in one of the larger joints instead of the usual symmetrical distribution, which usually includes the smaller joints, may lead to confusion. With this mode of onset an infection such as suppurative arthritis or tuberculosis is naturally suspected and treated accordingly. The fate of the three patients who presented in this manner serves as a warning. One had had his hip explored, the second received anti-tuberculous drugs for three months and the third was immobilized in plaster for an appreciable period, before the true nature of the illness became apparent.

Another type of arthritis has been termed *intermittent hydrarthrosis*. In this variety, of which there have been five examples in our series, the knees became distended with fluid at irregular intervals. The swelling persisted for a few weeks or many months and then disappeared spontaneously. The skin temperature over the joints was normal; there was no pain and the movements were not greatly impaired. Fever was usually absent, lymphadenopathy and leucocytosis were not observed, and the sedimentation rate was normal or slightly raised. A rash was present in only one case, and this was urticarial and atypical. Intermittent hydrarthrosis has long figured in the literature (Cohen, 1955) and its aetiology is still debated. The disorder in children should always be regarded as a possible forerunner of rheumatoid arthritis later in life, and the histology of a synovial biopsy may demonstrate changes compatible with this disease. Moreover in four of our five patients other joints subsequently became involved, although not seriously, and there was pain and limitation of movement. The final outcome is shown in Table 1. Three of the children have had no recurrence for nine years or more and are well; in the other two there is some disability which, in one case (E.S.), is kept under control with steroids.

Laryngeal Stridor. Arthritis of the crico-arytenoid joints has been described in long-standing rheumatoid arthritis in adults, causing stridor, dyspnoea and cyanosis (Hart and MacKenzie, 1955; Copeman, 1957; Baker and Bywaters, 1957; Pearson, 1957; Manning, 1957). We have been unable to discover any account of this occurring in children, but the present series includes three instances. Hoarse, laryngeal, inspiratory stridor was noticed, which became so alarming in one child that tracheotomy had to be performed after laryngoscopy had demonstrated 'paralysed' cords. The condition eventually resolved on cortisone and did not recur when this treatment was stopped.

Pericarditis. In his original description Still emphasized the importance of recognizing pericarditis. It may be obvious at the very outset and bear close resemblance to that occurring in rheumatic fever, the child being very ill, although endocarditis is not detected and myocarditis is less in evidence. More often it is insidious and overshadowed by the high fever, extreme malaise, vomiting and extensive polyarthritis. Pleuropneumonic signs may also be present. For instance, in one child who died of bulbar poliomyelitis a year after the onset of her rheumatoid disease, autopsy revealed unsuspected obliterative pericarditis and pleurisy.

It might be imagined that pericarditis augurs ill for the child's future, as it so often does in rheumatic fever, but this does not necessarily follow. In the present series, apart from the case already mentioned, one other child with clinical pericarditis died, but four others with this complication were all perfectly well when re-examined several years later. Although two are left with limited joint disability, none of them have any detectable cardiac disease and they are able to lead active lives. The favourable result in three of these children may have been due to steroid therapy given systemically. In one case it was injected into the pericardium. The fact that pericarditis in Still's disease is not usually associated with endocarditis and myocarditis must also have some bearing on the prognosis.

TABLE 1

INTERMITTENT HYDRARTHROSIS

Patient	Age at Onset (yrs)	Total Duration (yrs)	Result	Age at Last Examination (yrs)
C.G.	9	2	Complete recovery	12
E.T.	10	½	Complete recovery	12
P.S.	2	4	Complete recovery	13
S.T.	5	6	Recurrence after one year's intermission	12
E.S.	5	10	Recurrence after five years' intermission	15

Irido-cyclitis. This is fortunately a rare complication. It occurred in five patients in our series. Although local and systemic steroids appear to render the uveitis less active, vitreous and corneal opacities may form eventually and a cataract can develop. In this event surgery is not very satisfactory. Vision therefore becomes seriously impaired, even though arthritis may disappear entirely. One unfortunate boy in this group, now aged 19, was originally treated with gold, but has become a hopeless cripple, and has had to undergo enucleation of one eye because of this serious complication.

Lenoch, Králík and Bartoš (1959) questioned a true relationship between iridocyclitis and rheumatoid arthritis in adults. In Still's disease there is no doubt about this eye complication, which we observed in 5% of our cases and Ansell and Bywaters (1959) noted in 7% of theirs.

Amyloid Degeneration. This complication has been described in long-standing adult rheumatoid arthritis. Fortunately it is seldom encountered in children, but it occurred once in our series and has also been reported by Forsyth (1960) associated with calcification of the digital vessels. Our case, a boy with Still's disease at 18 months, developed albuminuria at the age of 5 years. The Congo red test was positive and a gland biopsy revealed amyloid changes. A further gland biopsy repeated six years later was normal. His arthritis improved after repeated intra-articular injections of hydrocortisone, and now at the age of 15 he plays rugby football, boxes and is leading a normal school life. There is minimal limitation of movement of the hips and shoulder joints, and the blood sedimentation rate is normal, but some albuminuria persists (200 mg./100 ml.). He has improved remarkably from a complication which is generally considered to have a very poor prognosis.

Muscular Abscess. The muscles in Still's disease usually escape the general inflammatory process; in fact all that is seen is wasting, depending on the degree of arthritis and immobilization. Acute inflammation of the soft tissues with swelling of the limb must therefore be a rare and remarkable complication. One such patient has been observed, in whom a lump in the biceps became necrotic and incision liberated a quantity of sterile pus. At this stage the child was critically ill with high fever, but made a spectacular recovery on cortisone. Now one year later his arm is normal in size and function, while arthritis of the knees and ankles remains. The pathogenesis of such lesions is obscure, but they may be areas of degenerating intramuscular nodular formation (Curtis and Pollard, 1940; Steiner, Freund, Leichtentritt and Maun, 1946; Kersley, Barber, Cregan and Gibson, 1954).

Nodules and Bone Erosions. Nodules are a well-recognized feature in rheumatoid arthritis and they were found in seven children. Three of them are now quite well with no disability; three still suffer, from a 'smouldering' arthritis and one died. One child, now 12 years of age, still has nodules, although she is otherwise well and is studying ballet dancing. The nodules have persisted for nine years, except for an intervening period of two years, during which they could not be detected.

Nodules are commonly subcutaneous, but they may be present in other regions. Possibly the following case is an example of nodules in bone. A girl of 6 years complained of pain and stiffness in the shoulder joints and cervical spine. Rash, adenopathy, pyrexia and moderate leucocytosis followed and the sedimentation rate was raised. One month later painless lumps were noticed on the forehead and over the occiput. Radiography of the skull revealed a number of irregular areas of bone destruction, not only in the region of the soft tissue swellings, but also scattered about in the parietal bone (Figs. 6 and 7). After numerous investigations had failed to reveal the nature of the lesions, a bone biopsy demonstrated a condition suggestive of a collagen disorder (Fig. 8). Steroid

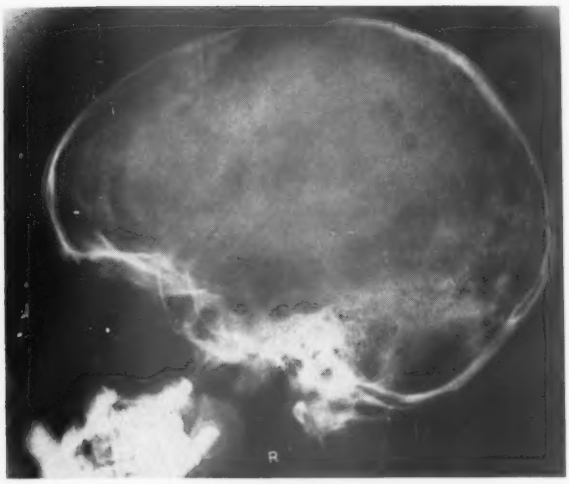

FIG. 6.—Radiograph of the skull of a girl, 7 years of age, with mild rheumatoid disease, showing irregular areas of bone destruction.

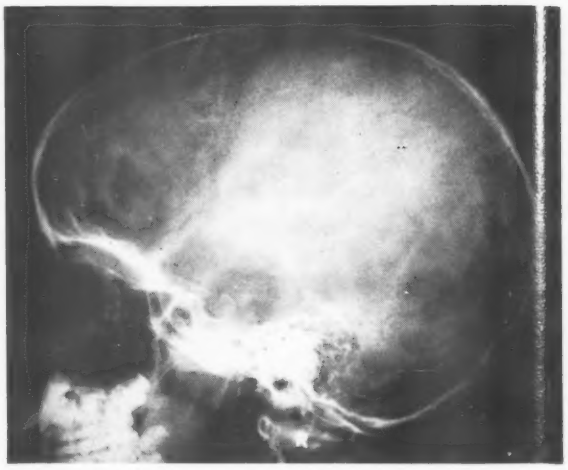

FIG. 7.—Radiograph of the skull of the same child (*c.f.* Fig. 6) two months later after steroid therapy.

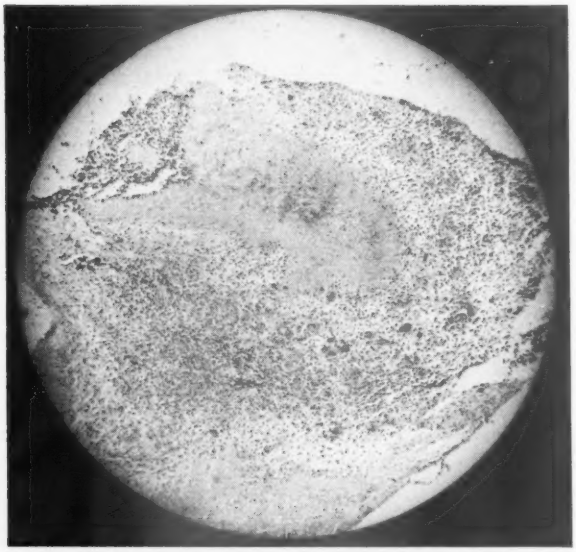

FIG. 8.—Histology of swollen subcutaneous tissue in the vicinity of the skull erosions depicted in Fig. 6. Degeneration of collagen can be seen with fibrinoid changes and the appearance of epithelioid cells and fibroblasts. (× 35.)

therapy caused the soft tissue swellings and the skull erosions to disappear, but twice there was a recurrence of both a few months after the treatment was stopped. On each occasion the skull radiograph returned to normal following a further course of steroids. Cystic bone lesions in rheumatoid arthritis have also been described by Mather (1954) and by Silver and Steinbrocker (1954).

Associated Collagen Disorders. With full knowledge of the clinical similarity between Still's disease, disseminated lupus erythematosus, polyarteritis nodosa and dermatomyositis, considerable care has been taken in selecting cases for this review. L.E. cells are difficult to find, but when they have been demonstrated that case has been excluded. Muscle biopsy, carried out in some instances, has also helped in the differential diagnosis.

Dermatomyositis was present in three of the children with Still's disease. In addition to the usual joint signs of rheumatoid disease, complicated in one instance by pericarditis and pleurisy, the children's hands appeared cyanosed, and telangiectases were visible in the nail beds and along the gum margins. In two, subcutaneous nodules were present, which on biopsy revealed rheumatoid changes. In all three children the skin and subcutaneous tissues had the thickened, non-pliable character of dermatomyositis, and this was confirmed in one by muscle and skin biopsy. Leucocytosis was not a feature, although the sedimentation rate was raised and there was ample evidence of general systemic involvement. Re-examined four to nine years from the onset, two of these children are quite well and attending school with little or no residual arthritis, and the third is happily at work despite some restricted movement of the joints. Curious reddish 'collodion' patches are still present on the knuckles of one child.

Associated Rheumatic Disease. Despite reports of the association of rheumatoid and rheumatic disease, this occurred in only one of the 100 cases, a boy of 9 years who developed chorea and carditis after rheumatoid arthritis had been present for

five months. He is now 14 years old and well without having had steroid therapy.

PART 2: TREATMENT

Rest followed by physiotherapy and graded activity form the basis of treatment for rheumatoid arthritis. Spontaneous remission on this regime may occur quite early. This, however, may not be maintained and after remaining free of symptoms for some months, 11 children in our total series suffered a relapse. Under such circumstances, or when simple measures fail, steroid therapy should be considered. In view of the disappointing reports of cortisone treatment in rheumatoid arthritis in adults (Joint Committee Reports, 1954, 1955, 1957a) and in children (Ansell *et al.*, 1956), it is important to record the good results obtained from steroids in the present series.

Steroid Therapy

Dosage. Sixty-three patients were studied, 60 of whom received steroids systemically and three by intra-articular injection alone. The majority were given oral cortisone, but some had A.C.T.H. injections and latterly prednisolone was used in preference to cortisone. The dosage of steroid and the duration of treatment depended upon the patient's response and upon the time taken for the disease to become inactive. The initial dosage was high, namely in the region of 200 mg. of cortisone by mouth daily for a period of at least a week. During the following two weeks it was gradually reduced to about 100 mg. daily and this dose was continued until the arthritis was well controlled. The child was then allowed up for increasing periods, and further reductions of cortisone were cautiously made until a maintenance level was reached below which symptoms recurred or there was a sharp rise in blood sedimentation rate. This was usually in the region of 50 to 75 mg. daily. It was found that severe relapses often occurred if each successive drop in dosage was too great or too rapidly undertaken. Maintenance therapy was usually continued for several months at least, and finally it was possible to taper off the steroid treatment entirely without provoking a relapse. In some instances, a short course of A.C.T.H. was given at the stage to stimulate the suprarenal glands, although this precaution was probably unnecessary provided the cortisone was withdrawn sufficiently gradually.

Delay in Treatment. Our figures show to a striking degree the importance of instituting steroid therapy during the first six months of the disease if optimal results are to be obtained (Table 2). Indeed, all of the 18 children so treated progressed favourably; 16 were perfectly normal and two were only slightly disabled once the attack had subsided and steroids had been withdrawn.

Duration of Treatment. Analysis of the 63 cases who received steroid therapy shows that three had intra-articular cortisone only, five died and four were taken off steroids for various reasons while the disease was still active. These cases are omitted from Table 3, which gives the total duration of treatment for the 38 patients in whom a remission of the disease took place and for the 13 patients still on treatment when the follow-up was completed. Among the 38 patients who had been treated with steroids on a dosage indicated above and for periods mentioned in Table 3, 32 (84%) had a remission of their disease within one year of starting therapy and a further four, totalling 36 (95%) within 18 months. No further steroids have been given to those 38 children, but the fact that 13 patients are still maintained on this treatment demonstrates that sometimes much longer courses are required. For example, one boy has now been on steroids for eight years as relapse occurred every

TABLE 2
DELAY IN SYSTEMIC STEROID TREATMENT AND FINAL DISABILITY: 38 CASES IN REMISSION

Final Disability Following Remission	No.	Time Before Steroid Treatment			
		< 6 mths	< 1 yr	< 2 yrs	> 2 yrs
None	24	16	4	3	1
Slight	9	2	1	1	5
Moderate	3	0	1	0	2
Severe	2	0	0	1	1

TABLE 3
DURATION OF SYSTEMIC STEROID TREATMENT

Duration of Treatment	No. of Cases	
	In Remission	Still on Steroids*
— 2 mths	7	1
— 4 mths	7	—
— 6 mths	7	2
— 8 mths	5	—
—10 mths	1	1
—12 mths	5	1
— 1½ yrs	4	3
— 2 yrs	—	2
— 3 yrs	—	1
— 4 yrs	2	—
— 7 yrs	—	1
— 8 yrs	—	1
Totals ..	38	13

* Many have been on treatment for a considerable time and the outcome is uncertain.

TABLE 4
TIME SINCE COMPLETION OF SYSTEMIC STEROID TREATMENT

Time Since Completion (yrs)	No. of Cases in Remission
−1	7
−3	16
−5	6
−7	9
Total	38

TABLE 5
PRESENT STATUS OF 60* CHILDREN GIVEN SYSTEMIC STEROIDS

Disability of Joints	Remission		Active	
	Nos.	%	Nos.	%
None	24	60·5	3	17·6
Slight	9	23·8	6	35·2
Moderate ..	3	10·5	4	23·5
Severe	2	5·2	4	23·5
Total ..	38		17†	

* Five children are dead.
† Thirteen of the 17 active cases are still under treatment with steroids, in one because iritis is still troublesome, although there is no arthritic disability.

time the dose was reduced below a critical level. The duration of treatment required in any individual child cannot be foretold and does not depend upon the severity of the initial manifestations. The fact that 18 months' treatment was adequate for the majority of the children contrasts with the years of treatment usually required in adults (Joint Committee Reports, 1954, 1955, 1957a). This difference in response is of great practical importance. More than one course was also necessary in some children to deal with recurrences of their disease several months or even years after steroid therapy was stopped. After five years' remission, however, relapses were unusual and Table 4 should be studied with these reservations. This Table gives the time that has elapsed since the child ceased to have steroid treatment and has remained well.

Results of Steroid Therapy. Steroid therapy produced some improvement within a week in the majority of children treated. The erythrocyte sedimentation rate usually fell to normal in about two to three weeks and the children were then allowed up. In many the effect of the drug was dramatic. Fever quickly subsided and the child's appetite and well-being improved. The lymph glands and the spleen, if enlarged, diminished in size, and a rapid decrease in joint pain and swelling led to improved mobility. Signs of pericarditis in a few children disappeared and recovery took place. Anaemia was gradually corrected without the necessity for blood transfusions. Only the skin rash proved resistant to treatment and continued intermittently after other manifestations of the disease had been controlled. With steroid therapy there was little doubt that the acute phase of the disease became much more tolerable and, while this in itself was gratifying, the long-term results were even more important. By modifying joint stiffness and swelling it proved possible to prevent serious permanent damage in the majority of children. The present status of the children treated with steroids systemically is seen in Table 5. In the 63 children treated systemically or locally, 41 have completed their steroid treatment (Table 6) and 35 (85%) of these are normal or show only slight residual joint damage. Seventeen patients still have active disease;

TABLE 6
COMPARATIVE SERIES

Series	Treatment	No.	Died		Active		In Remission		Final Disability: Cases in Remission							
									None		Slight		Moderate		Severe	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Present	No steroid therapy*	37	2	5	2	5	33	90	18	55	10	30	3	9	2	6
Present	Steroid therapy	63†	5	8	17	27	41	65	25	61	10	24	4	10	2	5
	Total ..	100	7	7	19	19	74	74	43	58	20	27	7	9	4	5
Colver (1937) ..	No steroid therapy	49	12	24	18	36	19	38	11 (58%)				8 (42%)			
Ansell and Bywaters (1959)	Steroid therapy in 63	(216) assessment in 209	9	4	105	50	95	46	42	44			53 (56%)			

* Compared with those on steroid therapy in the present series the majority of these cases were less severely affected.
† Includes three who received intra-articular therapy alone.

13 of them are on steroid therapy at present and the outcome is uncertain.

Five children died, two due to generalized rheumatoid disease with pericarditis and three from intercurrent infections. One of the two children, who died with pericarditis, relapsed after steroid therapy was stopped (in 1951) more abruptly than would now be recommended, and the other was not responding to a moderate dose of steroid when she died. With regard to fatal infections, one child developed bulbar poliomyelitis at a time when her Still's disease was well controlled with A.C.T.H.; her case was fully reported at the time by Pugh (1952). Another child died suddenly at home of bronchopneumonia following measles one month after hormone therapy had been stopped, and the third succumbed to infective hepatitis while on cortisone.

Intra-articular hydrocortisone has in some cases helped to clear up persistent joint effusions when given alone or in conjunction with oral cortisone. Two out of three children with joint effusions but no systemic signs who were treated with intra-articular injections responded promptly. A 25 mg. injection given twice proved effective, but in the third child this had to be repeated many times before the effusion in the knee joint responded. Some relief lasting six to eight weeks has been reported by Chandler, Wright and Hartfall (1958) from this method of treatment in adult cases. However, in spite of clinical improvement the joints deteriorated radiologically, possibly due to 'a damaging level of performance by interference with a normal, locally protective mechanism' (Chandler and Wright, 1958). In the two children just mentioned where this method succeeded the joints were clinically and radiologically normal six months and three years later respectively.

Toxic Effects of Hormones. Children receiving high dosage or prolonged steroid therapy should be protected against possible electrolyte disturbances by the administration of potassium chloride, 1 to 2 g. daily. A high protein and limited carbohydrate diet is also desirable in view of the protein loss produced by steroids. In face of the increased appetite it is difficult to reduce the total calorie intake although amphetamine may be of some assistance. Prevention of obesity obviously helps to minimize the strain put on weight-bearing joints. It is well known that infections may be masked by steroids. Oral penicillin (phenoxymethyl penicillin 125 mg. b.d.) may help to prevent the more common pyogenic disorders and should be prescribed daily.

These were the routine supportive measures adopted in the majority of cases and no serious electrolyte disturbance occurred. There was no undue tendency towards minor infections, and none developed tuberculosis. One child, however, contracted pneumonia and empyema following measles and made a complete recovery. The three deaths from infections have already been noted.

Euphoria was fairly common and in some ways was an advantage in helping the child to cope with a long illness. None of the children became depressed, as has been described in adult patients on steroid therapy. No significant glycosuria was noted and symptoms suggestive of peptic ulceration were not encountered. Hypertension occurred in two boys, necessitating the withdrawal of steroid therapy, after which the blood pressure returned to normal.

Osteoporosis due to cortisone affects the whole skeleton, but is most noticeable in the vertebral column. Involvement of the lower thoracic and the lumbar vertebrae occurred in eight children, 12·7% of those who had been treated with steroids, with associated deformity in five. One had spondylitis at the onset of his illness, which may have contributed to the osteoporosis, but in the other seven it was certainly due to steroid therapy. This complication, originally mentioned by Welch and Forsyth (1953), has been considered by Luder (1954), and was observed in two children by Ansell *et al.* (1956), although it was not referred to in adult trials (Joint Committee Reports, 1954, 1955, 1957a). When vertebrae were affected, it was thought desirable to keep the children ambulant to prevent further decalcification resulting from bed rest. In every instance recalcification occurred satisfactorily after withdrawal of cortisone and no neurological complications occurred. For example, one boy who developed vertebral collapse after a seven months' course of cortisone was able to play cricket for his school four years later and now at the age of 19 has a perfectly normal vertebral column with no evidence of permanent damage (Fig. 9a and b).

Routine x-ray examination of the spine every few months in children on long courses of hormone therapy was instituted in order to detect the complication early, and it was usual to reduce the steroid dosage, or stop it altogether, if increasing osteoporosis was found. It was noticed that children who already suffered from generalized skeletal decalcification due to enforced immobilization before steroid therapy were especially liable to vertebral collapse in a comparatively short period after treatment had begun. A high protein diet,

FIG. 9a.—Radiograph showing osteoporosis and vertebral collapse in a boy aged 12 after seven months' treatment with steroids.

FIG. 9b.—Radiograph of the spine seven years later (*c.f.* Fig. 9a) demonstrating that these lesions are no longer present.

extra calcium and vitamin D cannot be relied upon to prevent this complication. The use of testosterone or its analogues has also proved disappointing. Our experience with triamcinolone in a few cases has not shown it to be superior in this respect.

Other Forms of Drug Therapy

Phenylbutazone proved too toxic when tried in a few patients and mepacrine and chloroquin had no effect. Chrysotherapy was not used because of its known toxicity, but it should be mentioned that two children treated by a colleague improved considerably with gold therapy following only partial relief with steroids.

Many of the children received aspirin in ordinary analgesic dosage. Ten were given higher doses of aspirin (1 grain per lb. body weight per day), such as are sometimes employed in the treatment of acute rheumatic fever. This treatment was carried on for two weeks in nine children and four months in one without noticeable benefit. In three, clinical salicylism occurred with tinnitus, deafness, vomiting and acidosis, but despite this the blood sedimentation rates were above 50 mm./hr. and the joints remained swollen and painful. Another child developed severe bleeding due to salicylates. In our experience even high doses of aspirin failed to produce in any child the direct beneficial effect on the swelling and stiffness of the joints seen with steroid therapy.

DISCUSSION

This study confirms Still's original contention that the disorder in childhood often has its major impact on various sites of the body apart from the joints. It is indeed the inflammatory process in these tissues which provokes such an acute reaction and, if allowed to progress, it may eventually prove fatal. It has been shown that systemic involvement can in fact continue for a considerable time before arthritis becomes the most arresting feature, and that this has often delayed a correct diagnosis.

Both in its earlier age of onset and more isolated attack on one part of the heart, the pericardium, Still's disease is in marked contrast to rheumatic fever. But there are several points of similarity, such as nodules, the behaviour of the rash, the effect of trauma and the benefit obtained from

steroids. It is therefore surprising that rheumatic and rheumatoid manifestations were only once associated in the 100 cases. Other collagen disorders, however, were present at the same time in several.

Although Still believed that cases in which the joints alone were affected were not in the same category as the disease he described, our experience indicates that they can be regarded as a variant of the same disorder. We have seen that in many children there may be a 'systemic' stage followed by an 'arthritic' stage, but in a number the disease can begin insidiously in the joints, as it usually does in adults. Finally, adults occasionally fall ill with all the manifestations of the acute generalized onset most common in childhood. The first to describe this was Chauffard, a contemporary of Still.

Taking all these possibilities into consideration, there is no doubt that the malady is more acute in children than in adults and yet the period of activity of the disease is often very much shorter. For example, out of 60 patients in our series who were given systemic steroids, remission took place in at least 53% within one year of starting therapy. In the joint clinical trial of the Medical Research Council and the Nuffield Foundation (Joint Committee Report, 1957a) the remission rate in 53 adults treated with cortisone was only 23% over three and a half years. For the child with rheumatoid arthritis, therefore, a limited course of hormones may prevent permanent disability without incurring the dangers associated with years of steroid treatment.

Some writers believe that large doses of aspirin are as good as steroid therapy in the control of rheumatoid arthritis, and that the side-effects of steroids make their use undesirable. We have not found even high doses of aspirin to be nearly as effective as adequate steroid therapy. In the joint clinical trials of the Medical Research Council and the Nuffield Foundation (Joint Committee Reports, 1954, 1955, 1957a), in which it was concluded that cortisone was not superior to aspirin in the treatment of early rheumatoid arthritis in adults, the average dose of cortisone was on the whole much lower relative to the weight of the patient than that used in our series of children, where the amount was determined by the effect on the disease. It seems likely that success with steroids depends upon adequate dosage maintained over a sufficient period. In the Medical Research Council trial of 1954 (Joint Committee Reports, 1954) it was observed that a number of patients relapsed when steroids and aspirin were withdrawn rapidly after 12 weeks' treatment, whereas both drugs afforded greater relief when they had been given for one year or more.

Prednisone used in relatively higher doses in adults gave better results (Joint Committee Reports, 1957b), and the most recent trial (Joint Committee Reports, 1959) shows definite benefit from the use of prednisolone compared with aspirin or other analgesics. In the group treated with prednisolone a decrease in the incidence and progression of radiological signs of erosive joint disease was apparent. These findings are in favour of prednisolone being used in preference to cortisone. A trial combining prednisolone with corticotrophin is being carried out and may prove to be the best method in those cases requiring prolonged steroid therapy (Savage, Davis, Chapman, Wickings, Robertson and Copeman, 1959).*

In our experience, aspirin in high dosage has produced toxic effects including tinnitus, deafness, acidosis, vomiting and bleeding. As has already been pointed out, the one important side-effect of steroid therapy in our series was osteoporosis, affecting eight children out of the 60 treated systemically. This risk, however, was considered justifiable in view of the danger of death or severe crippling if the rheumatoid disease was left uncontrolled. Moreover, the vertebral lesions disappeared if steroids were stopped or their dosage reduced appreciably.

The results of treatment, both conservative and with steroids in our series of 100 children are given in Table 6. Although detailed records of the 37 children who were not given steroids are available and show a high remission and recovery rate, they cannot be used for comparison because they were not selected at random. Moreover, they were milder cases and this was the main reason they were only given symptomatic treatment. 'Historical' controls are also unsatisfactory, but, nevertheless, the results in our more severe cases treated with steroids are much better than those reported by Colver (1937), using the general measures, which were all that were available at that time. Deaths are now much less common and there are many more complete recoveries.

Sixty-three of our 100 children were given steroids. Ansell and Bywaters (1959) have reported 216 children with rheumatoid arthritis, of whom 63 were treated with steroids, i.e. about half the proportion as compared with our series. Fewer remissions were reported in their patients and the percentage

* Recently we have been successfully using this method of combining oral prednisolone with daily ACTH gel intramuscular injections. By this means a lower satisfactory total dosage of steroids is required and cortical adrenal atrophy is less likely to occur.

who had no final disability once the disease was no longer active was also smaller (Table 6). It is tempting to speculate that our apparently better results were due to the more frequent use of steroid therapy.

These comparisons are admittedly open to criticism. Nevertheless, clinical experience has convinced us of the value of steroid therapy when serious systemic disease or severe joint disturbances persist after several weeks' trial of conservative measures. The present study of 100 children with this disorder suggests that this therapy will have to be considered in about two-thirds of the cases.

SUMMARY

The most important systemic features and complications of Still's disease are described in addition to unusual types of arthritis, which may obscure the diagnosis.

Some support is given to the conception that rheumatoid arthritis is only one of a group of collagen disorders by the association in certain instances of Still's disease and dermatomyositis in the same patient.

Treatment with steroids gives the best results if begun early. The duration of treatment required is much shorter in children than in adults. Osteoporosis with vertebral collapse is the most serious complication of steroid therapy. Although a few recalcitrant cases pursue a relentless course in spite of all forms of treatment, steroid therapy is justified in all but mild forms of the disease and is most likely to bring about complete recovery.

Our thanks are due to the many colleagues who have allowed us to follow up their patients and to the practitioners who have given us up-to-date information about a few of the children. We are grateful to Dr. Martin Bodian for his histological reports and to Mr. Derek Martin for the photographs.

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SEROLOGICAL INVESTIGATIONS INTO SEQUELAE OF SCARLET FEVER WITH PARTICULAR REFERENCE TO RHEUMATIC FEVER

BY

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The question of detecting the changes in reactivity after streptococcal infections and before the first rheumatic attack is of great importance from the standpoint of rheumatology. This paper reports the results of our serological investigations after scarlet fever in a two-year follow-up of 31 children. Examinations, using nine laboratory tests, useful in rheumatology as indices of inflammation and immunobiological equilibrium, were carried out.

From the beginning of 1957 to the middle of 1959, 31 children with scarlet fever were treated for six days with penicillin and were followed up clinically and with laboratory tests. Sixteen of them were examined in the first 10 days of the disease, and tests were carried out later, after complications, in 15 cases.

Five children were 4 or 5 years old at the time they caught the disease, 23 were between 6 and 10 years, and three were between 11 and 13 years of age.

Three children were followed up for 10-12 months after the onset of the scarlet fever, two for 16-18 months, 12 for 20-24 months, and another 14 for 25-31 months.*

The disease took a comparatively mild course in all 31 children, but only four (13%) of them had neither complications nor intercurrent infections during the post-scarlet fever period. With the remaining 27 children (87%) the following complications were observed mainly during the first two months after the onset of the scarlet fever: tonsillitis acuta or tonsillopharyngitis chronica exacerbata in 20 cases (14 children underwent a tonsillectomy), arthralgias in eight cases (four having had arthralgias before scarlet fever), transient E.C.G. and clinical signs of myocardial involvement in three cases, lymphadenitis colli in five cases, otitis media in three cases and allergic manifestations in five cases (including a case with bronchial asthma).

The clinical and laboratory observations were carried out on each child at different intervals because of technical difficulties; the mean number of laboratory tests performed on each child was nine.

Methods

The laboratory tests were carried out using the following methods:

Erythrocyte sedimentation rate. The E.S.R. was determined by Westergren's method (1921, 1957), estimations up to 10 mm. in the first hour being accepted as normal.

C-reactive protein. This was determined by the method of Anderson and McCarty (1950), using C.R.P. anti-serum† and assessed as −, +, ++ or +++, in accordance with the criteria suggested by Wuhrmann and Wunderly (1957).

Serum protein fractions. These were determined by paper electrophoresis following Flynn and De Mayo (1951), and total protein by Kingsley's method (1940). Normal figures for sera from 42 healthy children (Popov, Stanisheva and Kostova, in the press) are set out below:

Serum Protein Fraction	Relative % ($\sigma = 1$)	Serum (g./100 ml.) ($\sigma = 1$)
Albumins	56·4±3·1	3·93±0·37
Globulins α_1 ..	4·3±0·8	0·30±0·08
α_2 ..	10·3±1·1	0·72±0·14
β ..	12·4±1·5	0·87±0·13
γ ..	16·6±2·0	1·16±0·17

Plasma fibrinogen levels. These were determined by the kjehldalometric method; the normal range was 180-350 mg./100 ml. plasma and was in accordance with our own findings (Popov and Stanisheva, 1958).

Antistreptolysin reaction (A.S.O.). This was determined by the method described by Kalbak (1947).

* After the completion of the work another clinical and laboratory check was carried out and the term of observation was prolonged to three years.

† Manufactured by Schieffelin and Co., New York.

Standard serum from the State Serum Institute, Copenhagen, was used. Though a titre of over 200 units was accepted as pathologically increased, we have previously shown (Popov and Bojadzieva, 1957) that serial estimations have a very much greater value than a single initial determination.

Haemagglutination reaction. Here the Waaler-Rose reaction was used as modified by Svartz and Schlossmann (1952) according to Dickgiesser and Harter (1953). A titre of over 16 units was accepted as increased.

Coombs test was carried out (Coombs, Mourant and Race, 1945).

Atypical anti-erythrocyte agglutinins: agglutinating and conglutinating (in 6% dextran solution) auto- and isoantibodies at +4°, +22° and +37° C.

Tissue antibodies. These were determined by the antihuman globulin consumption method of Steffen and Schindler (1955).

Results

The first clinical group of six children (Cases 1-6) was characterized by comparatively mild scarlet fever, but with various complications and intercurrent infections in the post-scarlet fever period. In this same group several complications were observed especially during the period within the third and sixth week after contracting the disease. During this period, as well as during the subsequent period, tonsillitis and tonsillo-pharyngitis occurred with frequent exacerbations. In two children (Cases 1 and 2) these inflammations lasted for more than a year and subsided after systematic penicillin treatment and tonsillectomy. With the second case the tonsillectomy resulted in a temporary turn for the worse, clinically (a severe pharyngitis) and in the laboratory findings. The combined antibiotic treatment and tonsillectomy with Cases 3 and 6 shortened the period of reconvalescence. Four of the children had shown allergic manifestations since early childhood, which were considerably aggravated after the scarlet fever. Case 6 had a relapse of scarlet fever seven months later. This 5-year-old child showed quite a number of allergic and septic complications (besides the usual children's infectious diseases and an infectious mononucleosis). Parallel to the clinical developments the laboratory tests showed deviations from normal with a great number of peaks (Fig. 1). The tests for activity of the inflammation were positive in all children of this group as were the signs of streptococcal sensitization. Not one of the cases in the first group developed rheumatic fever during the observed period.

The second group consisted of 15 children (Cases 7-21). They also had mild scarlet fever. During the first three to five weeks temporary complications were observed, mainly persistent tonsillitis and tonsillo-pharyngitis, which necessitated penicillin treatment and tonsillectomy in seven children. During the following months the post-scarlet fever period was undisturbed, with only slight intercurrent ailments. The laboratory findings showed some deviation from the normal during the period of the complications, but the curves ran almost unchanged. No case of rheumatic fever was seen in this group of children.

The third group consisted of 10 children (Cases 22-31), considered as controls as they showed little symptomatology during the post-scarlet fever period and almost constantly normal laboratory findings (Fig. 2). Tonsillectomy was performed on three children. Here also no cases of rheumatic fever occurred.

During the time of the influenza epidemics (1957 and 1959) 21 children fell ill. The period of the disease passed mildly without complications. In 10 cases temporary changes were noted in some of the laboratory tests used.

The individual laboratory tests in this clinical material showed the following results:

Erythrocyte Sedimentation Rates. Constantly normal results were obtained in 12 children, while in 19 the E.S.R. was raised to a varying degree. The highest figure for the first hour was 52 mm. and more than 40 mm. in five children on isolated occasions. The raised E.S.R. was seen in connexion with complications of various kinds, e.g. severe tonsillo-pharyngitis, bronchopneumonia and mononucleosis. In two children (Cases 1 and 4) it was sustained for three months at a pathological level, and in another child (Case 2) up to a year.

The results indicate that the E.S.R. figures were highest during the first two months. In single estimations significant deviations were established up to the 12th month. During the following months, even with clinical signs of activity, the E.S.R. rarely surpassed the normal boundaries (the exceptions were in cases of mononucleosis and other severe complications).

C-reactive Protein Test. As a sensitive indicator of inflammation this test revealed interesting data during the different stages of the post-scarlet fever period. Negative results were obtained in only 11 cases. During the first 10 days the C.R.P. was positive in 10 of 16 cases investigated. The greatest number of positive results were seen during the period of the complications, i.e. the third to the sixth week. Up to the ninth month only in odd cases was the test positive, being usually + and rarely ++ (and linked with frequent exacerbations

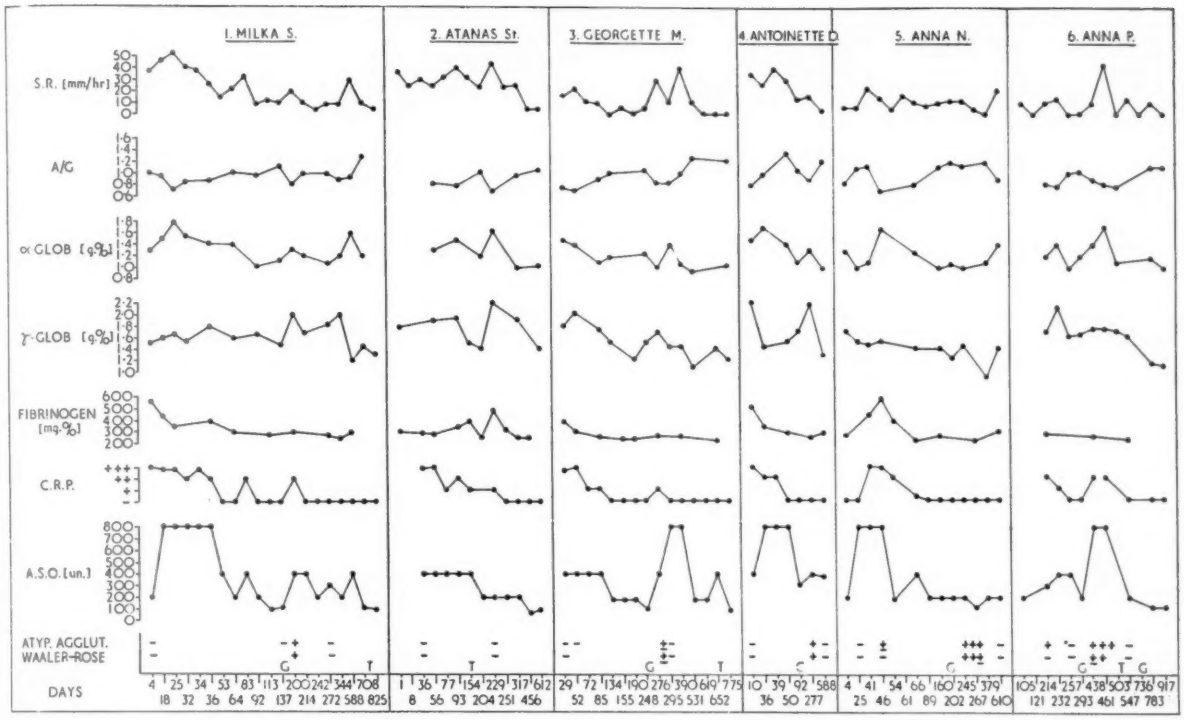

FIG. 1.—Summary of the laboratory tests on Cases 1-6. G = Influenza; T = Tonsillectomy.

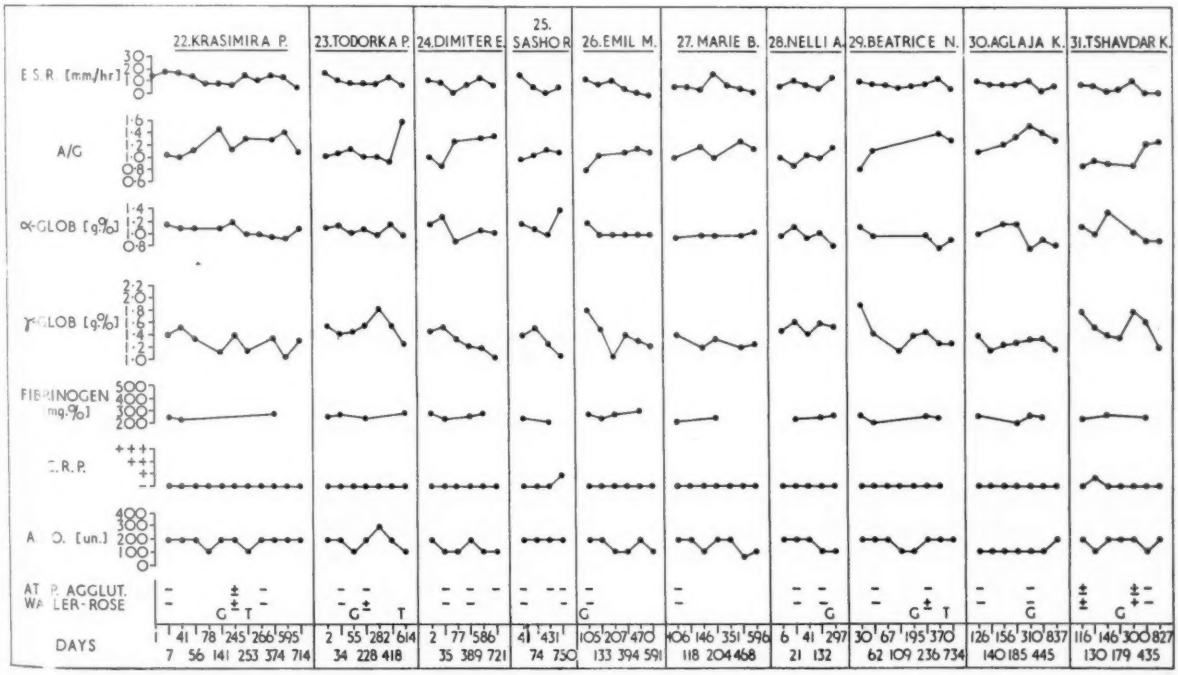

FIG. 2.—Summary of the laboratory tests on Cases 22-31. G = Influenza; T = Tonsillectomy.

of an inflammation in the throat). At the end of the observed period a positive test occurred only in a few cases (in bronchopneumonia, mononucleosis and after tonsillectomy). After the ninth month even with clinical signs of active inflammation like tonsillo-pharyngitis the test remained negative. In cases with numerous complications (Cases 1-6), the estimation of C.R.P. during the time of activity showed a positive result repeatedly and the curve remained positive for a month or longer. A detailed analysis revealed that the test showed a positive result in active inflammation and then it quickly abated to become positive again with a new exacerbation. During the later stages of the post-scarlet fever period the test became scarcely positive even in an active inflammation.

Serum Protein Fractions. In 16 children the protein fractions were constantly normal, and in 15 children a moderate disproteinaemia was established. But even in Cases 1-6 the albumin levels rarely dropped below 45%, α_2 globulins did not surpass 6·6 relative % (0·52 g. %) and α_2 globulins reached maximal up to 15·8 relative % (1·31 g. %). The β globulins did not undergo significant changes. The most marked increase in the serum protein fraction levels occurred with the γ globulins, which increased early and remained high for a long time, reaching 26·5 relative % (1·85 g. %). From Fig. 1 it can be seen that the curves of the albumin/globulin ratio and of α and γ globulins show an irregular fluctuating course. These variations in the serum protein fractions correspond to the fluctuating course of the complications of infections of the mouth and throat as well as to the intercurrent infections.

The variations of serum protein fraction levels indicated a fluctuation of α globulins chiefly during the first six weeks after the scarlet fever onset, being increased later only in odd cases with severe complications. The γ globulins were increased during the first 10 days and remained high for some months (in eight children up to five months and in some cases up to one year). During intercurrent infections and especially in influenza, changes took place only in γ globulins.

Fibrinogen Levels. In none of the cases was a plasma fibrinogen level over 600 mg. % recorded. In the plasma of six children a fibrinogen level of 400 to 600 mg. % was found: Case 1 on the fourth day of the disease, Case 2 on the third day after tonsillectomy, Case 4 on the tenth day of the scarlet fever, Case 5 on the 46th day, the period usually associated with complications, Case 12 on the 14th day and Case 19 on the 44th day in a severe tonsillo-pharyngitis.

Antistreptolysin Reaction. In 12 children the reaction was normal, and in 19 it was raised: being up to 400 units and up to 800 units in 10 and nine children respectively. Of nine children with raised A.S.O. five belonged to the group with numerous complications (chiefly of streptococcal type). The A.S.O. curve in this group remained at its high level for varying periods of time. In Case 4 a normal value was not established during 20 months. The greatest frequency of high titres was found between the third and the sixth week and in cases of persistent active inflammation of the throat. In the period after the second month the A.S.O. was raised only in a few cases.

Haemagglutination Reaction. During the post-scarlet fever period the test was positive in seven cases only after influenza.

The Coombs Test. The direct Coombs test was constantly negative; the indirect Coombs test was slightly positive in two cases after influenza and in a single case of infectious mononucleosis.

Atypical Agglutinins. These, with slightly or moderately raised titre, were found for a short time in four cases after influenza and in one case of infectious mononucleosis.

Tissue Antibodies. These were not found in the serum of any child.

The laboratory tests showed that symptoms of inflammatory and immunological type were found in 21 children, most clearly manifested in Cases 1 to 6. The laboratory changes in our 21 cases differed from those of the rheumatic attack (severe dysproteinaemia, hyperfibrinogenaemia and a raised A.S.O. titre) and were as those in infectious diseases, mainly with an increase of the γ globulins, slight and transient changes in the α globulins, normal or slightly raised fibrinogen levels, etc. There was no evidence of significant involvement of the connective tissue as in rheumatic fever. The immunological tests showed signs of streptococcal sensitization in 19 children, A.S.O. being slightly raised in 10 of them, and in the remaining nine children reaching 800 units. The raised level of the A.S.O. was likely to be caused both by the scarlet fever itself and by the different complications mainly of streptococcal origin. It is worth noticing that the A.S.O. in four children out of 21 who had had

influenza showed a non-specific raised titre of the type of the anamnestic reaction.

There was a parallel between the clinical manifestations (mainly focal inflammations) and the laboratory findings during the first six months, but later changes in the immunobiological condition were rarely found in the presence of clinical symptoms.

In our series we had no experience with scarlet fever patients who had not been treated with penicillin.

Summary

Thirty-one children with scarlet fever treated with penicillin were followed up for more than two years, systematic laboratory tests (E.S.R., C.R.P., S.P.F., fibrinogen level, A.S.O., sensitized sheep cell reaction, the Coombs test and reaction for tissue antibodies) being carried out.

In 21 children immunobiological changes were related to the numerous complications and intercurrent infections observed in the majority of the cases during the first six months of the post-scarlet fever period.

The clinical and cardiological check as well as the laboratory tests showed no signs of rheumatic fever.

There was no ground for considering that the post-scarlet fever period was immunobiologically identical with the acute phase of rheumatic fever, nor with the period before the first rheumatic attack.

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FUNCTIONALLY ACTIVE INTRATHORACIC NEUROBLASTOMA

BY

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It is apparent that, under certain circumstances so far undefined, neuroblastomata may be associated with a secretion of pressor amines in sufficient amounts to cause significant symptoms. Mason, Hart-Mercer, Millar, Strang and Wynne (1957) reported an infant with an adrenaline secreting intrathoracic neuroblastoma which was successfully removed. The preoperative symptoms, sweating and pallor, were completely relieved by extirpation of the tumour. We wish to report on a child in whom we were able to reach the correct diagnosis before operation by referring to the description by Mason and his colleagues. The symptomatology, situation and histology of the tumour and the postoperative course were similar to the infant described by Mason *et al.* (1957). As these authors stated, the importance of these findings appears to lie beyond their immediate interest.

Case Report

C.H. was the second born child of healthy parents. She weighed 7 lb. 6 oz. at birth and was a full-term baby. She was regarded by her parents as quiet and easily manageable, apart from occasional episodes of vomiting, up to the age of 20 months. From about this age it was noted that each time the child was taken up from its cot (after its morning rest, at 10 o'clock at night and on rising in the morning) the pillow and pillow case were drenched. For some time it was thought that in spite of attempts to keep the child dry she was wetting the bed and pillow. The child's head was so wet that her hair was always stuck down on to her head and neck. During the day, especially after meals, she sweated profusely, especially noticeable on the upper lip and around the hair line, for no apparent reason. At the age of 2 she was treated for roundworms and from then until her admission to hospital at the age of 3 years 8 months she was described as a lazy child, content to be all day in her pram and be 'pushed around by the other children'. The sweating continued, more noticeable some days than others, but never causing severe prostration. The hair was always so wet that its texture was altered and its growth limited. Her mother never noted any loss of consciousness or fainting attack, but stated that at times the child seemed to go deaf and very pale in colour. On these occasions she seemed distant and uncooperative.

On admission to hospital the child weighed 26 lb. She was stunted, listless and apathetic. Her face was pale and beads of perspiration could be seen on the lips and forehead. Though not acutely ill the child seemed generally out of condition.

Another positive finding on physical examination was a fullness in the region of the posterior ends of the 11th and 12th ribs on the left side. This was caused by a firm irregular mass, apparently growing from the 11th intercostal space. This mass was neither tender nor fluctuant. A radiograph of the child's chest is shown (Fig. 1) and the relationship of the tumour to the 11th and 12th ribs in Fig. 2. Examination of the blood showed Hb 12·3 g./100 ml., the red cells normal, and white cells 8,300/c.mm. (lymphocytes 66%, polymorphs 24% and eosinophils 2%). The blood urea was 25 mg./100 ml., serum sodium 135 mEq/litre, serum potassium 4·6 mEq/litre and serum chlorides 100 mEq/litre. The faeces contained neither ova nor parasites. No abnormality was seen in a radiograph of the skull. A diagnosis of an adrenaline secreting intrathoracic neuroblastoma was made and the child was kept under observation in order to assess the extent of functional activity of the tumour, its daily variation and to assess factors promoting safe removal of the tumour. During this period of observation the child's temperature rose to 100° F. intermittently, the resting pulse rate varied between 100 and 140 per minute and the blood pressure between 95/50 mm. Hg and 125/65 mm. Hg. She did not appear to be more distressed one day than another, gave no indication of any extrinsic factor causing elevation of the blood pressure and generally the clinical impression was reached that adrenaline secretion was at a constant level. For most of the time the child lay in her cot apathetic and uncomplaining, always perspiring and at times quite profusely.

Urinary Assay of Catecholamines. The screening test suggested by Hingerty (1957) for catecholamines in urine was positive on three occasions. Visual comparison showed a urinary catecholamine excretion of 600 μg./24 hours and 1,140 μg./24 hours (expressed as nor-

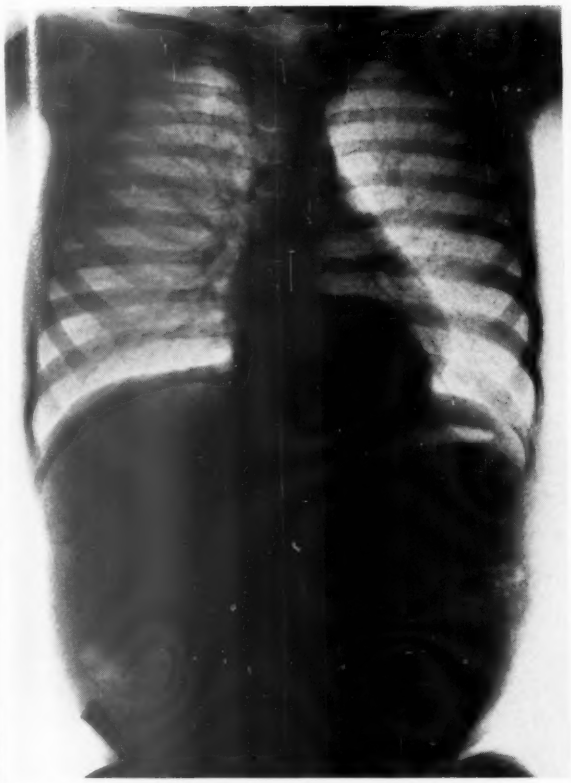

FIG. 1.—Radiograph of the chest immediately before operation. The tumour lies behind the heart shadow.

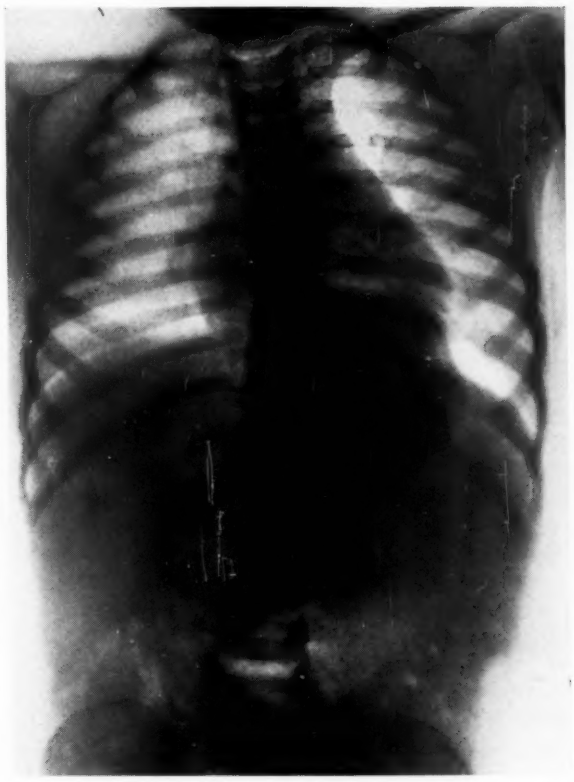

FIG. 2.—High penetration view to show erosion of posterior ends of 11th and 12th left ribs.

adrenaline) on two consecutive days. In adults the normal excretion of catecholamines is below 185 μg./24 hours. Mr. B. A. Callingham of the School of Pharmacy assayed the urinary pressor amines in a 24 hours' collection of urine and showed them to be 326 μg./24 hours (70% of the pressor amines were present as noradrenaline).

Operation. The child was 3 years and 10 months at the time of operation. She was premedicated with chlorpromazine 13·0 mg., promethazine 13·0 mg., pethidine 50 mg. and atropine 1/100 grain. Scoline 50 mg. intramuscularly was followed by oral intubation and anaesthesia maintained by nitrous oxide, oxygen and tubarine. Barbiturates were not used at any stage.

A curved incision was made over the tumour. The 11th and 12th left ribs with periosteum and the tissues in the intercostal space were mobilized intact and the pleural cavity opened. An extension of the tumour into the erector spinae muscle was mobilized and the firm lobulated main tumour, lightly adherent to the vertebral body, was dissected out. Its exact relationship to the sympathetic chain could not be identified, nor was it possible to be certain of the amount of residual tumour in the nerve filaments leaving the intervertebral spaces adjacent to the tumour. It did, however, seem certain that there was no intrathecal extension. The lower lobe of the lung was normal. The left kidney was not examined. The tumour, most of the 11th rib and the whole of the 12th rib were removed. The pleural cavity was closed without drainage by suture of the diaphragm to the 11th rib remnant. The blood pressure fluctuations during the operation are shown in the accompanying chart (Fig. 3). During the operation 360 ml. of whole blood were transfused. Within 24 hours of the operation the blood pressure became constant at 100/50 mm. Hg and the sweating ceased. Before the 10th day after operation the child had started to take more interest. On the 12th day Hingerty's screening test for urinary catecholamines was negative and biological assay confirmed a normal excretion of noradrenaline. The child progressed satisfactorily.

Pathology of Tumour. The tumour was examined in detail by Dr. D. F. Barrowcliff who reports:

'A coarsely lobulated tumour weighing 125 grams and measuring 7 × 7 × 4 cm. (Fig. 4). The sulci are deep (up to 1 cm. in places). Two pieces of rib 3·5 cm. long are attached to one pole. Growth does not appear to invade ribs or intercostal muscles. The cut surface shows radial striations, is mostly pale fawn or grey, but is flecked with tiny spots of bright yellow material. The consistency to the cutting knife is moderately firm and in places gritty.

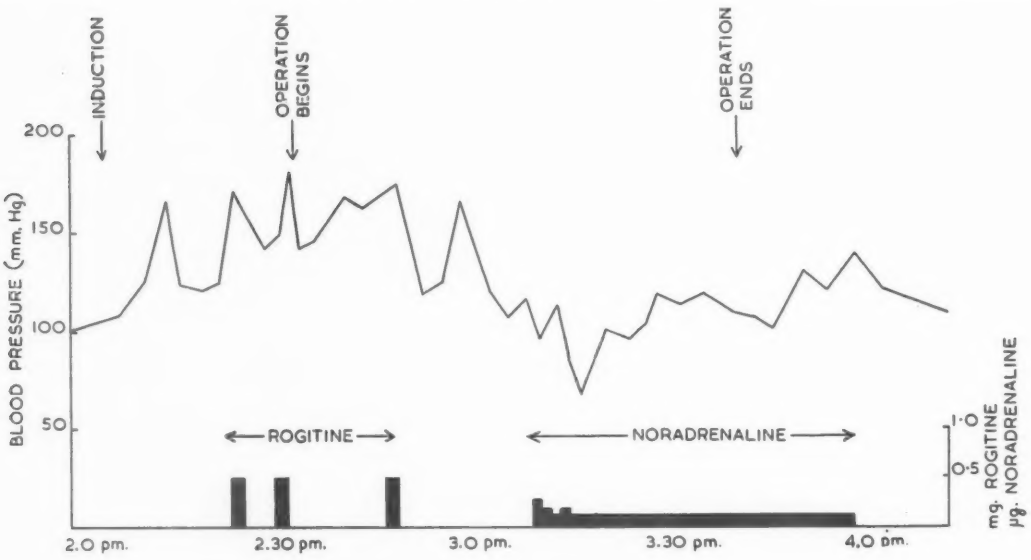

FIG. 3.—Chart of blood pressure fluctuation during operation.

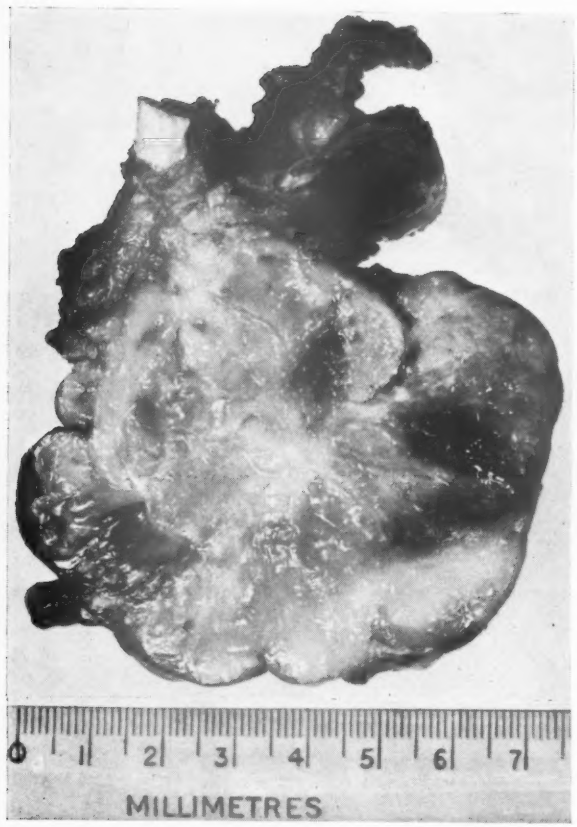

FIG. 4.—Cut surface of tumour. Portions of 11th and 12th ribs are attached to the tumour.

'Most of the tissue was fixed in formol-saline, the rest in Orth's fluid.

'Sections from a total of 20 blocks were examined.

'Representative slides were stained with haematoxylin and eosin, van Gieson, von Kossa, silver impregnation, periodic acid Schiff and toluidine blue.

'All sections show bundles or whorls of nerve fibrils which in a few places are closely packed, orderly and regular and studded with adult ganglion cells, resembling a ganglio-neuroma (Fig. 5). In most areas the nerve fibres are loosely arranged in irregular bands, and these bands enmesh groups or sheets of cells which vary from small darkly staining sympathogonia to large, nearly mature ganglion cells (Fig. 6).

'The last-named have a large nucleus measuring approximately 30 μ in diameter, with a prominent nucleolus and a radially-arranged chromatin network. Binucleate forms are not uncommon; many of the nuclei are eccentrically or peripherally placed. The cytoplasm is finely granular with a homogeneous ground-glass appearance. A few of the more mature forms show Nissl's granules.

'The cell which is considered to be intermediate between the sympathogonia and the mature ganglion cell is shown in Fig. 7. This is polygonal, has a finely eosinophilic cytoplasm, and a nucleus with a well-formed nuclear membrane. Amongst these lie smaller cells, some of which show a coarsely granular yellowish-brown pigment in their cytoplasm. Such chrome-positive cells are uncommon. When present they tend to occur amongst the less differentiated elements, none being found amongst the mature ganglion cells. Neighbouring nerve fibrils are sometimes similarly stained, though more faintly.

These intermediate cells occur in the largest foci,

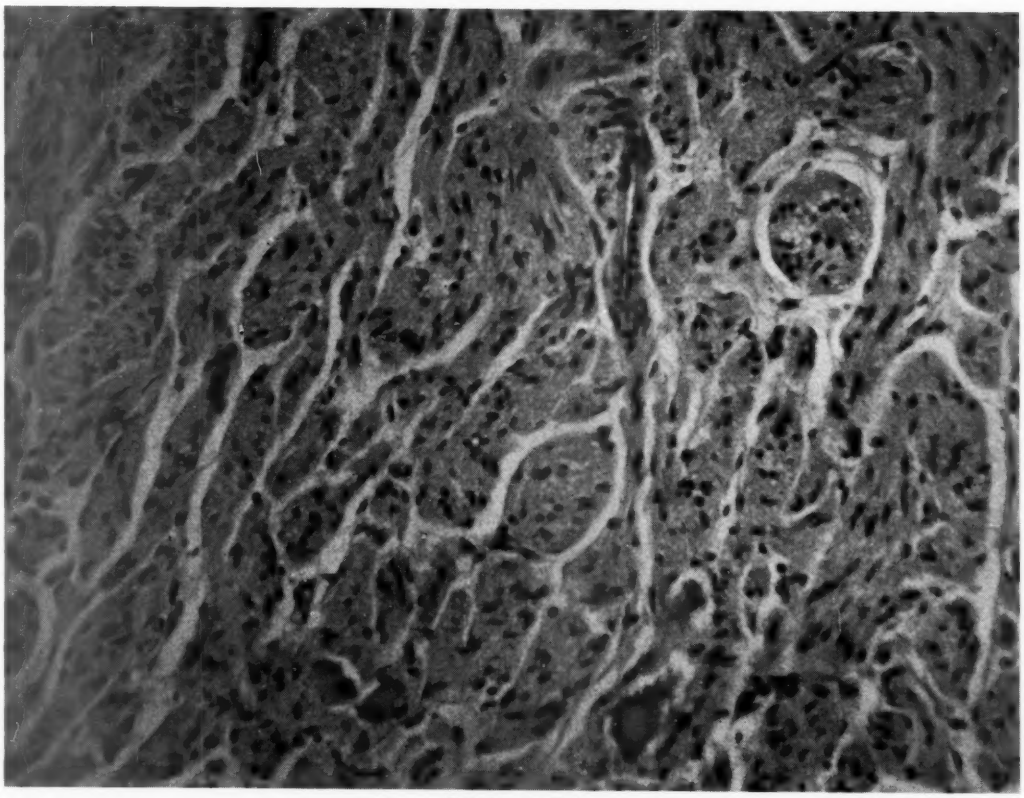

FIG. 5.—(× 76.)

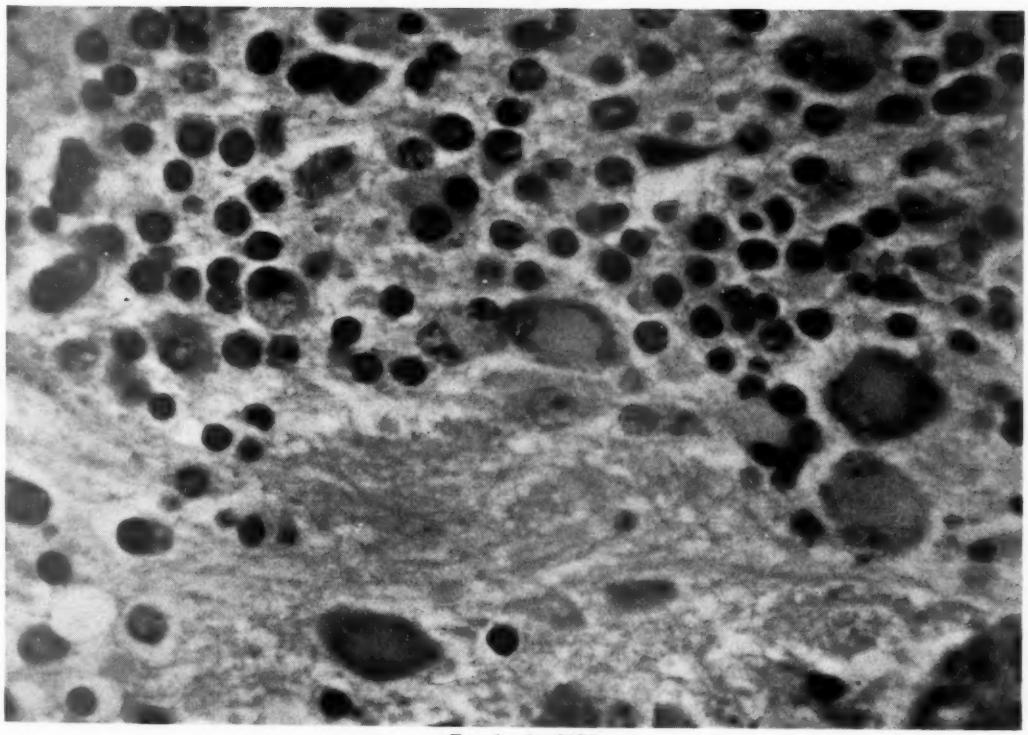

FIG. 6.—(× 215.)

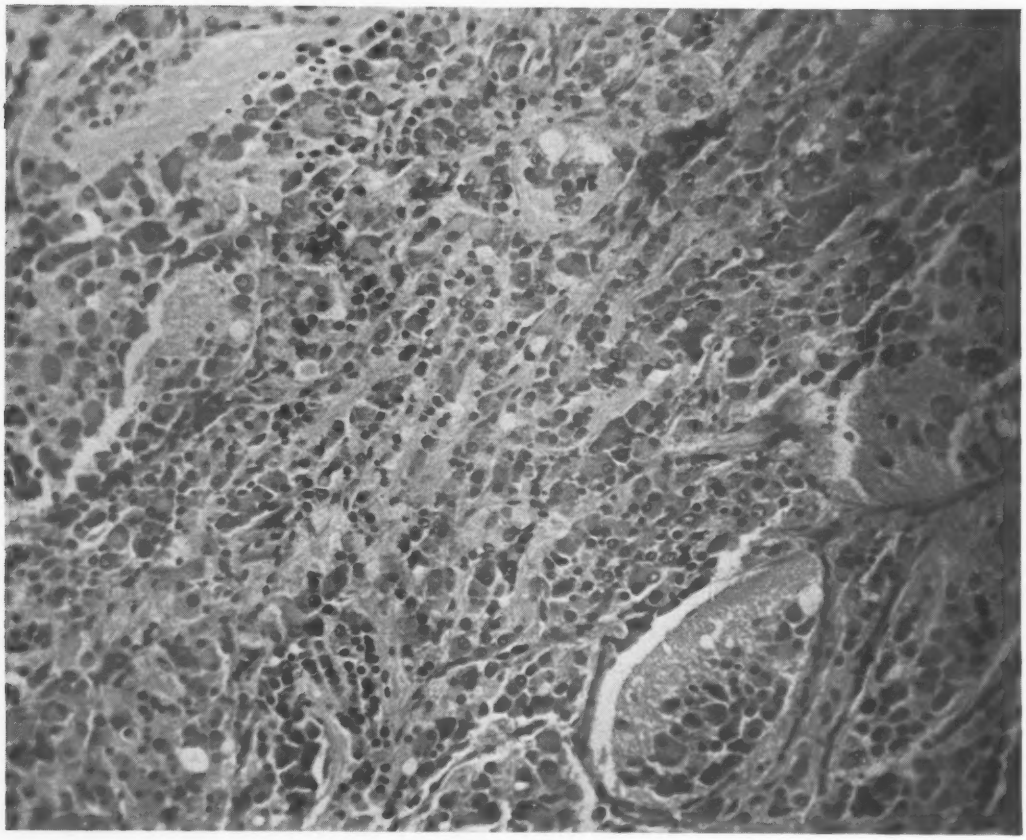

FIG. 7.—(× 54.)

often extending in solid sheets over several microscopic fields. The centres of such sheets may very rarely show necrosis. More common are islands of faintly calcified amorphous or crystalline material, apparently lying haphazardly throughout the tumour, but being found more often in areas where the more mature cell predominates.

'In a few areas only the tissue is composed almost entirely of masses of darkly staining small round cells, sometimes showing a peritheliomatous arrangement or forming the characteristic rosette of a neuroblastoma (Fig. 8). Frequently they are found, in small groups, intimately mixed with the intermediate cell or with the chrome-positive variety.

'Although the intermediate cell might be considered to be a phaeochromoblast, or precursor of the phaeochromocyte, the failure to demonstrate any chrome-positive material in such sheets of cells, perhaps coupled with the small total quantity of noradrenaline extracted from a tumour which consists mainly of such cells, is against such hypothesis. Further, the development of such intermediate cells into mature ganglion cells can be seen from a study of several areas of the tumour, whereas no mature phaeochromocytes can be identified.'

Assay of Catecholoamines in the Tumour. Acid extraction of the tumour and alumina absorption of catecholoamines showed a concentration of 235 μg./g. of tumour by biological assay.

Subsequent Progress. Fifteen months after operation, the child was well. There was no sweating, blood pressure was 100/50 mm. Hg and the Hingerty test was negative. There was no evidence of secondary deposits from the tumour.

Discussion

In attributing functional activity to this neuroblastoma a number of factual points must be considered. Unless a tumour such as this is examined by serial section in its entirety its total cell content remains questionable. Gradations between the normally functionless neuroblastoma and the fully differentiated ganglioneuroma are, of course, not unusual, and are reported by various authors as ganglioneuroblastomas; this would, perhaps, be a more accurate designation of the tumour we describe. Reference may be made to Russell and Rubinstein (1959) for current opinion on differentiation and functional activity in nerve tissue tumours. These authors stated that progress by cellular differentiation to a phaeochromocytoma in

th· neuroblastomas was rare, but had been recognized since Wahl's (1914) report; they also mentioned the paper by Fernando, Cooray and Thanabalasundram (1951) describing neuroblastic elements in a functionally active phaeochromocytoma. In addition they stated that in the case of Mason *et al.* (1957) the portion of the tumour used to confirm the presence of pressor amines might possibly have been the portion containing phaeochromocytes. Describing three patients with noradrenaline secreting neuroblastomas, Isaacs, Medalie and Politzer (1959) concluded that neuroblasts themselves were responsible for the secretion of catecholamines or for the hyperstimulation of normal chromaffin tissue, and that if the former was acceptable it implied that chromaffin tissue was not essential for the production of catecholamines. The potential complexity of the cell content of any tumour originating from the primitive neural crest must inevitably make classification difficult, although it is easy to understand how more than one element can be represented. The tumour reported here is of interest clinically inasmuch as, although it behaves as a phaeochromocytoma, it is essentially a malignant ganglioneuroblastoma. Only to this extent can this report add information on the origin of the catecholamine secretion. Endless speculation is possible on the findings in this patient, and we shall discuss only two points. First, reasons for the fact that catecholamine secretion in neuroblastomas has only recently been recognized and second the bearing of functional activity on the prognosis.

A likely reason for Mason's *et al.* (1957) case being the first reported is that the biological assay of catecholamines is itself a recent introduction and that previously no method was available to detect functional activity had this been suspected. However, it does seem odd that in the 44 personal cases of neuroblastoma described by Koop, Kiesewetter and Horn (1955), the 80 cases reviewed by Ware (1956) and the 22 personal cases of intrathoracic neuroblastoma and ganglioneuroblastoma

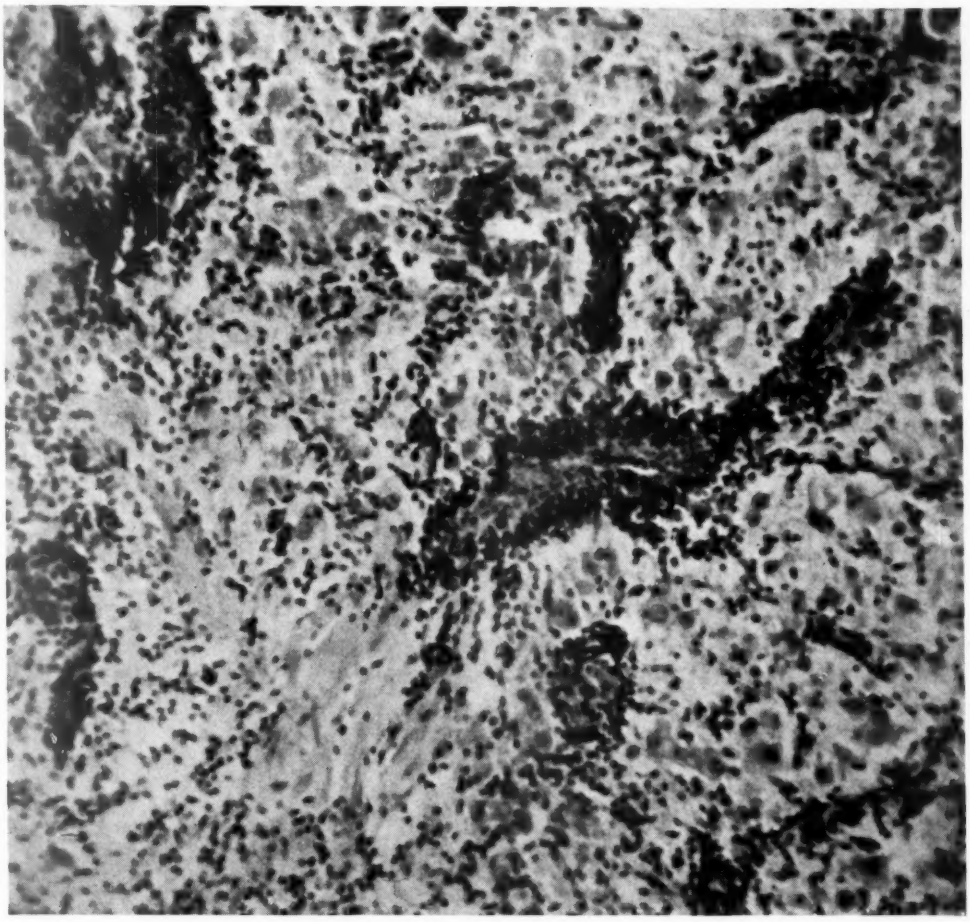

FIG. 8.—(× 76.)

reported by Schweisguth, Mathey, Renault and Binet (1959), neither elevation of the blood pressure nor excessive sweating is recorded in a single instance. If the condition is so uncommon it seems difficult to explain the reporting of a number of cases, including the present one, since 1957.

It seems safe to assume that functional activity has existed without being recognized, notably in the patient described by Alexander (1951) in which a brilliant result was obtained from operative removal of the neuroblastoma. The patient, a 3-month-old boy, was admitted to hospital in 1948. Profuse sweating was the only symptom. A radiograph of the chest revealed a shadow in the left lower zone. The tumour, reported as a highly cellular malignant growth arising from the sympathetic nervous system, was removed shortly after the infant's admission to hospital. He was free of symptoms on discharge from hospital one month after operation. James Thomson of Dundee, who originally referred the patient for surgery, has let us know the child's present condition (Thomson, 1960). The boy is now aged 11, has no recurrence of the tumour nor of the excessive sweating, and the blood pressure is 125/70 mm. Hg. The history, type of tumour and abrupt cessation of sweating after operation suggest the tumour was functionally active at the time of operation. An interesting, and possibly confirmatory, feature is that the tumour was in the same position in the thorax, namely the left lower zone, as in the case described by Mason *et al.* (1957) and our own. These three chest films, in fact, bear a striking resemblance to each other. In contrast, in the 22 cases reported by Schweisguth *et al.* (1959), in which no functional activity was present, none of the tumours they described was situated in this position in the thorax. Reverting to reasons for the recent recognition of functional activity in neuroblastomas, it is possible that this activity may be temporary and occurs only during a phase of the tumour's maturation. Thus it would be possible to explain the failure in the past to record excessive sweating over a number of years as a symptom. In modern practice sweating would be regarded as an indication for estimation of catecholamine levels in the blood and urine and functional activity would be confirmed by this method. Persistent pyrexia was recorded by Ware (1956) in 13 of the 80 cases recorded and in some of these activity may have existed, though sweating was not specifically described. It is difficult to imagine such gross symptoms arising from the presence of the tumour, as in our case, continuing till death and not being remarked upon if this functional activity once established does, in fact, continue to the time of the patient's death. On the grounds of the neuroblastoma's known tendency to revert toward the fully differentiated and, as far as is known, functionless ganglioneuroma, we postulate this reversion occurring spontaneously in the type of neuroblastoma under discussion, as part of the natural history of the tumour and that conceivably some of these tumours become symptomless ganglioneuromas of adult life. (This hypothesis is strengthened by the fact that although the prognosis appears unfavourable, the active neuroblastomas surgically removed have progressed well after operation.) Koop *et al.* (1955) considered the prognosis was good if the patient survived 14 months after excision of a neuroblastoma.

No patient living this period after operation subsequently died. Each of the intrathoracic adrenaline secreting neuroblastomas recorded (Alexander, 1951; Mason *et al.*, 1957; and the present case) have all survived this period in normal health. We take this to indicate that the tumour may be undergoing spontaneous reversion to the fully differentiated benign state during the period before operation, and had these children been observed over a longer period, functional activity might have ceased spontaneously. We mention this as a hypothetical possibility to explain certain features and not as a method of treating the disease. An explanation such as this may be a tortuous way of stating that a predominantly malignant tumour is more likely to exhibit functional activity than one predominately benign and fully differentiated, namely the ganglioneuroma. Greenberg and Gardner (1959) have reported a patient from whom a ganglioneuroma was removed. Before operation 148 μg. of neoepinephrine and 3·6 μg. epinephrine were present in the urine in a 24-hour period. After removal of the tumour the values fell to 17·1 μg. and 0·65 μg. respectively. (Such evidence complicates the hypothesis we put forward, but it could be argued that the urinary values of catecholamines were relatively low because the tumour was benign.) Until more facts become available, reasons for failing to recognize excessive sweating and raised blood pressure in certain non-chromaffin nerve tissue tumours before the description by Mason *et al.* (1957), must remain in doubt. There are so few cases of this disease reported that a late prognosis based on these reports must be unconvincing. In addition to the remote prognosis, operative removal of the tumour is likely to be more hazardous if the urine is found to contain raised levels of free pressor amines. Mason *et al.* (1957) described the methods they used to influence sudden

fluctuations of blood pressure during and immediately following operation. A similar routine was used in our case, except that our patient was not digitalized before operation. We can find no reference to unexplained death during operation on children with neuroblastoma and it is possible therefore, excretion of pressor amines notwithstanding, that the risks of operation are not materially increased. By contrast, removal of a phaeochromocytoma, accompanied usually by very much higher blood levels of pressor amines, is a grave undertaking. This difference can be explained by the different pressor amine content of the two types of tumour. The Hingerty (1957) test is a most useful test for the screening of these infants; it is speedy and sensitive. Sandler and Ruthven (1959) have shown that the urinary excretion of vanylmandelic acid (V.M.A.) is raised in patients with adrenaline secreting tumours and that the urinary V.M.A. determinations represent a more reliable method for ascertaining the presence of an adrenaline secreting tumour.

Summary

The clinical findings in a child with an intrathoracic neuroblastoma associated with excessive secretion of catecholamines are described. Reasons for the activity in such tumours being only recently recognized and the prognosis are briefly discussed. Details of the pathology of the tumour are presented.

We should like to thank Mr. B. A. Callingham of the London School of Pharmacy, Dr. D. R. Rigg who anaesthetized the child, and Dr. D. F. Barrowcliff for details of the pathology of the tumour. Mr. T. Skuse and Mr. L. Hine of the Central Pathological Laboratory, Warwick, prepared and photographed the specimen.

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A FAMILIAL TUBULAR ABSORPTION DEFECT OF GLUCOSE AND AMINO ACIDS*

BY

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The above title was used (Luder and Sheldon, 1955) to describe a family in which a renal tubular reabsorption defect involving glucose and amino acids appeared in three successive generations (female twins then aged 5, their father and his father). The purpose of this communication is to correct the impression given in the previous paper, to report some further investigations and to discuss the management of these cases in the light of recent treatment.

In the case of the grandfather, who was known to have had renal glycosuria for many years, an amino acid leak could not be demonstrated because the necessary technique was not known during his lifetime. But its existence is strongly suggested because he was very short and thin (weighing 98 lb.), and had an unexplained osteoporosis of his vertebrae.

This family thus provides strong evidence of a combined renal tubular reabsorption defect transmitted as a Mendelian dominant, a point of considerable interest to which we shall return later.

In 1955 a third daughter was born. Her urine was free of reducing substances and showed a normal amino-acid chromatogram, so that she did not suffer from the disease that affected her twin sisters. She died at 4 years of age from tuberose sclerosis, the autopsy also showing multiple hamartomata in the heart and kidneys and nephrocalcinosis. We are grateful to Dr. Darmady for microdissecting the kidneys; the 'swan's neck' deformity of the proximal tubule, as described in the de Toni-Fanconi syndrome, was not present.

The family were discovered because one twin (Lindsay) had been brought for advice regarding thirst and poor growth. She was found to be nearly 5 in. shorter than the other twin (Glynis) and this was attributed to a greater amino acid leak, although the blood group findings showed almost conclusively that the twins were uniovular. Neither twin showed any radiological evidence of rickets, and their serum phosphorus levels were 4·2 mg.% (Lindsay) and 5 mg.% (Glynis). These levels were considered normal, and the possibility of a tubular phosphate leak was not further pursued.

Both children had raised serum alkaline phosphatase levels ((Lindsay) 31·9 King Armstrong units and (Glynis) 27·2 King Armstrong units), but in the absence of clinical or radiological rickets and in view of the normal phosphorus levels, the raised phosphatase levels were tentatively attributed to a disturbance of liver function, rather than being regarded as a warning of potential rickets. The subsequent history of the children shows this view to have been incorrect, for when they were seen after an interval of three years the smaller twin had developed rickets, and the serum alkaline phosphatase had risen from 31·9 to 83 King Armstrong units; the other child still showed no rickets and the phosphatase level was unchanged. In both we have now been able to demonstrate a renal tubular defect of phosphate reabsorption and an acidosis of renal tubular origin.

Summary of History and Previous Findings

The twins, although apparently uniovular, were o different birth weights, Lindsay weighing 4 lb. 15 oz. and Glynis 5 lb. 15 oz. The smaller twin was seen at the age of 5 years because of stunting, thirst and poor appetite. Her height was 36 in., weight 23 lb. 14 oz. (both below the 3rd percentile), but no other physical abnormalities were present in any system, including the skeleton. The skeletal age was 3 to 3½ years. Blood chemical findings were normal except for the raised alkaline phosphatase, already mentioned. The only abnormal findings were in the urine, which contained an excess of many amino acids in a typical 'renal tubular' pattern, a small amount of protein and an excess of glucose.

The other twin, who was taller and heavier showed similar chemical findings, though the excretion of amino acids and glucose was rather less.

The father was tall and well built and excreted glucose and amino acids, but in slightly smaller amounts than

* Reporting the development of a tubular phosphate leak in a family previously described in this journal in 1955 (vol. 30. p. 160).

the twins. He had a serum phosphorus level of 3·2 mg.%. No radiological abnormality was seen in the bones, and the serum alkaline phosphatase level was normal (10 units % King Armstrong).

Lindsay

The smaller twin was not seen from 1954 until 1957 when, at the age of 8¾ years, she was brought on account of gradually increasing genu valgum. Although active and alert, she was very small for her age, measuring 42 in. (107 cm.) in height and weighing 33 lb. (15 kg.). The degree of genu valgum was such that with the knees touching, the medial malleoli were 4½ in. (12 cm.) apart, but there were no clinical signs of rickets. Radiological examination, however, showed typical rachitic changes at the ends of the long bones, and the bone age was retarded to 5 to 6 years. The heart was normal; blood pressure 115/75 mm. Hg. The other systems were normal and the urine contained a variable amount of protein and, as on the previous occasions, both glucose and amino acids, the amino acid chromotogram being very similar to that seen in other types of renal tubular defect. There were no Kayser-Fleischer rings and no cystine crystals in the corneae.

Blood chemistry. Analysis revealed calcium 9·5 mg.%: inorganic phosphorus 3·0 mg.%: alkaline phosphatase 83 King Armstrong units %: urea 37 mg.%: sodium 148 mEq/litre: potassium 3·8 mEq/litre: chloride 112 mEq/litre: bicarbonate 17 mEq/litre.

Renal investigations.

ACIDOSIS STRESS TEST. (1). This was carried out in July, 1958. The *p*H of urine before the test was 7·0 and 6·72. Ammonium chloride 6 mEq/kg./24 hr. was given in six-hourly doses for 48 hours. Urinary *p*H levels were then as follows: after 16 hours, 6·42; after 22 hours, 5·14; after 40 hours, 4·82. Plasma bicarbonate after 38 hours was 10 mEq/litre.

ACIDOSIS STRESS TEST. (2). This was carried out in November, 1958 using the technique described above. The results tabulated below show the levels at six-hourly intervals after the test dose.

Urinary *p*H.	Ammonia N. (mg./24 hr.)
6·56	49
5·14	78
5·16	76
5·52	70
5·76	74

Blood *p*H before test was 7·26 and 48 hours after test dose, 7·28.

UREA CLEARANCE. This revealed 34·6 ml./min./1·73 m.² or 63% average standard normal; blood urea, 50 mg.%.

GLOMERULAR FILTRATION RATE. This was 120 ml./min./1·73 m.², about 65% of normal.

PHOSPHATE CLEARANCE (endogenous). This was at a rate of 63 ml./min.

PHOSPHATE REABSORPTION. This was estimated by the method described by Anderson (1955) and showed the following results:

October, 1957, TmP=2·2 mg./min./1·73 m.² and in November, 1958, TmP=2·15 mg./min./1·73 m.².
(Normal 4·0–4·5 mg./min./1·73 m.².)

INTRAVENOUS PYELOGRAM. Both kidneys excreted a poor concentration of dye, but structural abnormalities could be excluded.

Glynis

The larger of the twins, Glynis was reinvestigated when just 9 years old. Like her sister she was an active and alert child, her height being 48¾ in. (124 cm.) and her weight 46 lb. (20·8 kg.). The urinary findings were similar to those of her twin. Clinical examination was normal, there was no radiological evidence of rickets, and the bone age was normal. Slit-lamp examination of the corneae showed no cystine crystals.

Blood chemistry. Analysis revealed calcium 9·9 mg.%; phosphorus 2·5 mg. %; alkaline phosphatase 30 King Armstrong units %; urea 30 mg.%; sodium 152 mEq/litre; potassium 3·9 mEq/litre; chloride 106 mEq/litre; bicarbonate 20 mEq/litre.

Renal investigations.

ACIDOSIS STRESS TEST. (details as for Lindsay). Urinary *p*H before test was 6·84 and 6·56. Urinary *p*H level after 16 hours, was 4·68; after 22 hours, 4·82; and after 40 hours, 4·68. Plasma bicarbonate after 38 hours, was 13 mEq/litre.

PHOSPHATE REABSORPTION. In January, 1958, TmP=3·6 mg./min./1·73 m.².

INTRAVENOUS PYELOGRAM. The excretion of dye was good and equal on both sides. The appearances were normal.

Urinary Protein Electrophoresis

It has been shown by Butler and Flynn (1958) that electrophoresis of the urinary protein in renal tubular disorders tends to show a distinctive pattern, characterized by a relatively high content of α_2 globulin and sometimes of β globulins as well, especially when the proteinuria exceeds a level of about 15 mg./100 ml. We are indebted to Dr. Flynn for investigating this point in both twins and their father.

The total urinary protein in the father was 40 mg./100 ml.; in Glynis it was 20 mg./100 ml. and in Lindsay 10 mg./100 ml. In all three the electrophoretic pattern was examined by Dr. Flynn, who reported it as being typical of renal tubular disease. Electrophoresis of the serum proteins in both twins showed a pattern normal for their age.

Treatment and Subsequent Progress

Lindsay. It was decided to try to control the genu valgum with walking calipers, while treating the rickets with vitamin D. The dose was initially 25,000 I.U. daily. After a week, some radiological improvement was evident at the wrist and the serum phosphatase level had fallen from 83 to 61 King Armstrong units. After two months, the level was 69 King Armstrong units. At this point the dose of vitamin D was increased to 50,000 units daily and was maintained for four months. She was

also given an inorganic phosphate mixture by mouth, made up of NaH_2PO_4 H_2O., 2·1 g. and Na_2HPO_4 12 H_2O., 30·0 g. plus water to 1,000 ml. The dose was 500 ml. daily (providing 1½ g. phosphorus daily).

After four months had elapsed, she was re-examined, and was found to have grown 2 inches. Genu valgum had lessened, and serum alkaline phosphatase had fallen to 40 King Armstrong units. Radiographs of the wrists some weeks earlier showed continuing improvement in the rickets. The plasma phosphorus however was still 2·5 mg.%. She was then changed to another phosphate mixture, made up of NaH_2PO_4. $4H_2O$., 78 g.; water to 950 ml.; 5N NaOH to 1,000 ml. (*p*H now 7·0). The dose was 40 ml. t.d.s.

This was continued for a further seven months and then stopped; at the same time, the daily vitamin D dose was progressively increased to 60,000 I.U., 75,000 I.U. and finally 90,000 I.U. over the next year.

During this period radiological healing of the rickets occurred and has been maintained until the present time (see Fig. 1). The genu valgum also disappeared. The child has continued to grow and gain weight (during the 18 months of treatment she grew 4 in. and gained 5 lb.). The serum alkaline phosphatase, early in the treatment, had fallen to 25 King Armstrong units, and now fluctuates between 35 and 45 King Armstrong units. The plasma phosphorus has varied between 2·8 mg.% and 3·5 mg.%, in general remaining stable throughout the period (Fig. 2). In spite of the high doses of vitamin D the serum calcium has remained normal. The blood urea has shown a tendency to rise, the most recent figure being 44 mg.% while no appreciable change has occurred in the sodium, potassium, bicarbonate, or chloride levels.

Glynis. Bearing in mind our experience with Lindsay, we decided to treat Glynis with an oral phosphate mixture with the object of preventing the onset of rickets, which in view of her raised serum alkaline phosphatase level seemed imminent. We also hoped to gauge the effect of this treatment by its influence on the phosphatase level.

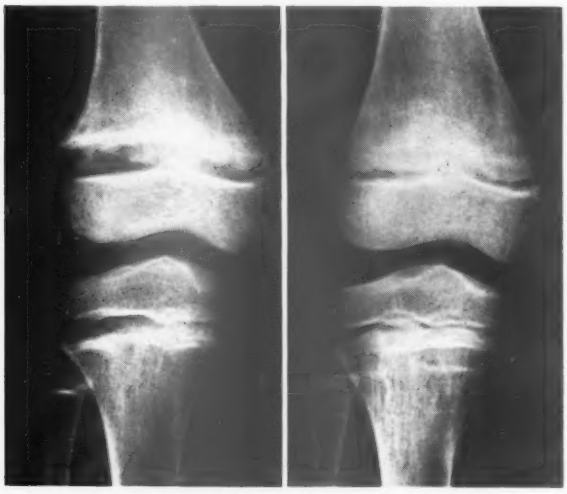

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FIG. 1.—Radiograph showing Lindsay's left knee; (a) August 29, 1957 (b) June 9, 1958.

She was given the first inorganic phosphate mixture (see above) for three months, by which time her serum phosphorus level was 3·5 mg.% and phosphatase level 26 King Armstrong units. She was then switched to the second mixture for a further three months. At the end of this period there was no detectable change in the child; the serum phosphorus was 3·8 mg.%, and phosphatase 32 King Armstrong units. The treatment had exerted no effect on the serum phosphatase level.

Phosphate treatment was then stopped and vitamin D was given in a daily dose of 25,000 units for five months. At the end of this time the serum phosphorus was 2·8 mg.%, having at one time reached 4·6 mg.% and the alkaline phosphatase had fallen to 23 King Armstrong units. Serum calcium remained normal. During the next three months the vitamin D was gradually raised to 50,000 units daily, but the phosphatase level after this course was still 27 King Armstrong units, and serum phosphorus 3·9 mg.% (see Fig. 3). No sign of rickets has appeared.

Discussion

It is now apparent that additional tubular disturbances are present in both twins, who were formerly thought to show leaks of amino acids and sugars only. These are (a) a phosphate leak (b) a defect in ammonia formation and possibly in H ion exchange.

This development raises several questions: (1) Are these tubular disturbances part of the original hereditary tubular reabsorption defect? (2) If so, why was their appearance so delayed? (3) Why has one twin developed rickets already, whilst the other has so far failed to do so?

The fact that serum phosphorus levels were normal at the age of 5 years is evidence against the existence of tubular phosphate leaks at that time. These must, therefore, have developed between the ages of 5 and 8 years, whilst the other leaks were probably congenital, to judge from the failure to thrive and the symptoms of thirst which dated from an early age. Such a delayed appearance of one of a number of tubular leaks is unusual, though not unknown. We have examined the records of 18 cases of low phosphate rickets, with or without other tubular leaks, seen at Great Ormond Street in recent years, and in no case could it be shown that the development of the various tubular leaks was separated in time. The first estimation of serum phosphorus was performed in all the cases before the age of 3 years, and in the majority before the age of 18 months. In all cases the level was abnormally low at the first estimation and continued to remain low thereafter. Nor have we any personal experience of the consecutive appearance of other leaks

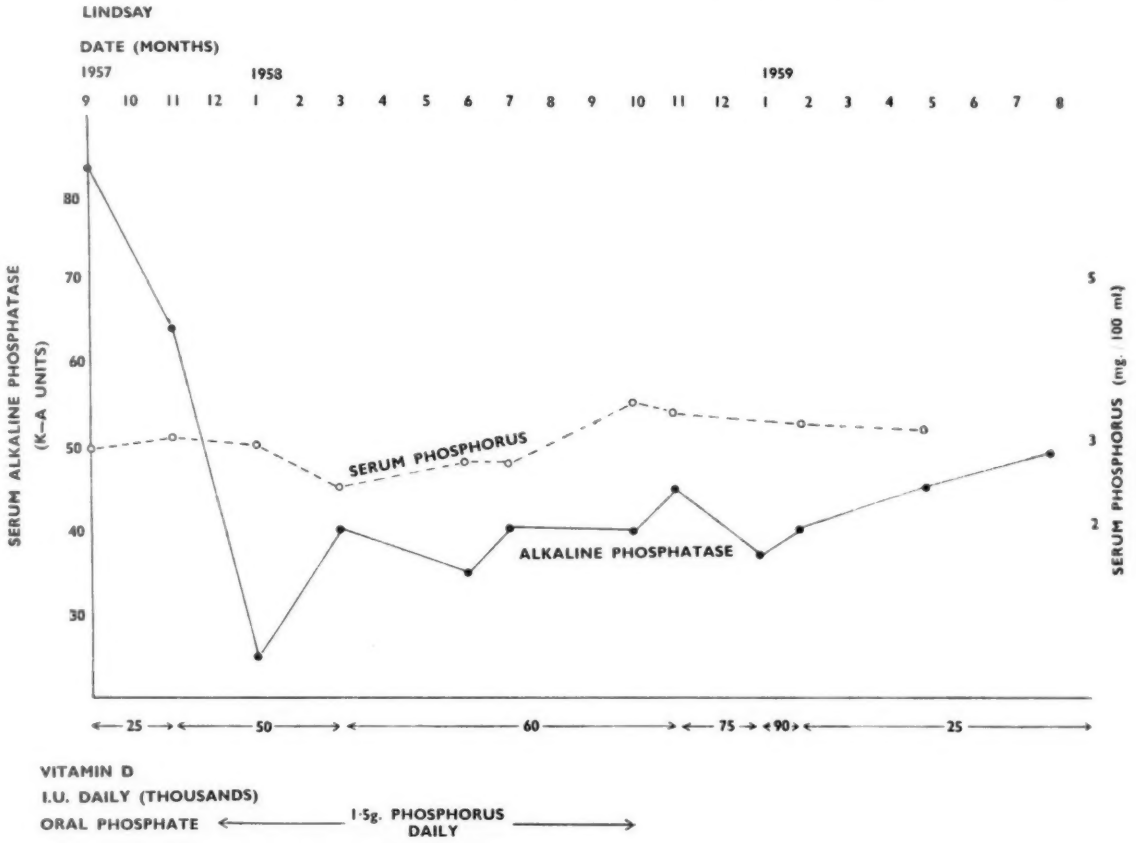

FIG. 2.—Lindsay; serum alkaline phosphatase and serum phosphorus levels during treatment with vitamin D and oral phosphate.

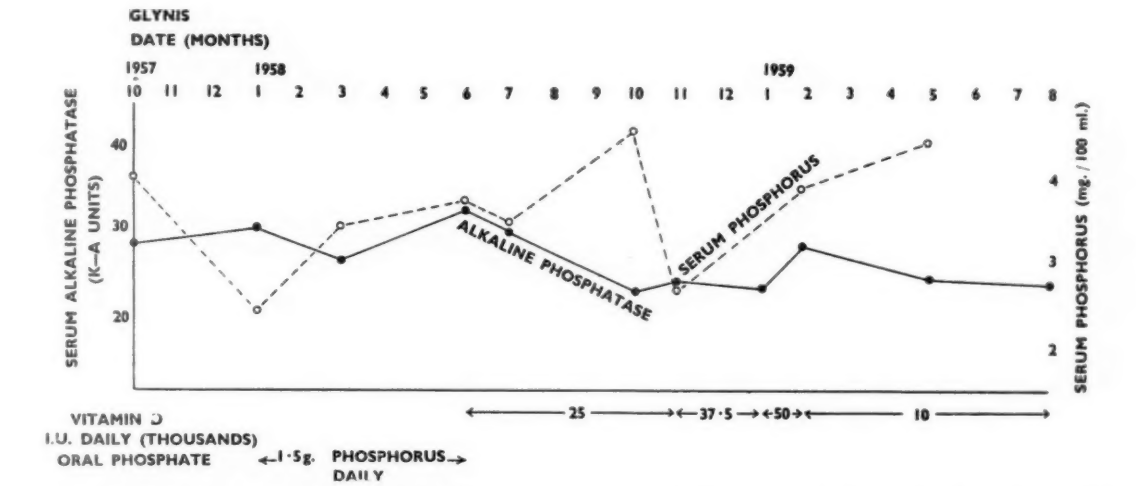

FIG. 3. Glynis; serum alkaline phosphatase and serum phosphorus levels during treatment with vitamin D and oral phosphate.

in cases of inherited renal tubular defects, though, of course, it is well known that the clinical manifestations arising from these leaks may be delayed for a considerable time. The other possible origin of the phosphate leak is from acquired damage to the renal tubules. Tubular reabsorptive defects can, of course, result from damage to the tubules by disease processes, infective, degenerative or toxic, or from lack of an essential substance. Thus pyelonephritis and chronic nephritis may result in leaks of sodium, chloride, potassium, amino acids, phosphate, glucose, bicarbonate and water. Toxins that may cause various leaks include lead, uranium, phloridzin and phenol compounds. In metabolic disorders such as Wilson's disease and galactosaemia, tubular amino-aciduria also occurs in the early years of life, presumably due to the toxic effects on the tubules of copper and galactose respectively. Vitamin D deficiency may cause a fall in phosphate reabsorption, and anti-diuretic hormone deficiency causes a water leak. In the absence of any history or urinary findings suggestive of kidney disease, the possibility must be considered that the damage has been caused by the long-standing amino acid leak, especially the essential amino acids. It had previously seemed likely to us that this constant depletion accounted for the dwarfing of one of the twins. Any kidney damage of this nature is likely to affect glomeruli as well as tubules, and it may be significant that the blood urea of the rachitic twin has tended to rise since 1954. The other renal function tests, namely the urea clearance, glomerular filtration rate and intravenous pyelogram all show evidence of diminished glomerular efficiency. The acidosis stress tests also indicate impaired ability to acidify the urine after a load of an acid salt. The other twin, Glynis, who had a lower amino acid excretion in 1954, is less dwarfed, has a better phosphate reabsorption (though still abnormally low) and her glomerular function tests are normal.

The tests of ability to acidify the urine after doses of ammonium chloride indicated considerable impairment in the case of Lindsay, particularly in the second test (November, 1958). Her plasma bicarbonate concentration and blood *p*H were both low before the test, and the test showed that the power to form ammonia was much decreased. In the case of Glynis the results were less striking, but her plasma bicarbonate concentration was slightly low before the test and fell considerably during it. Lindsay therefore has an acidosis and Glynis an 'incipient' acidosis, due to a defect in the tubular mechanism for H ion exchange and ammonia formation. It is conceivable that these tubular disturbances could be explained by the effects of the original amino acid leak, though it must be confessed that there are strong arguments to the contrary. The total loss of amino acids in the urine in these cases is small compared with the dietary intake and is unlikely to have any adverse clinical effects unless it comprises mainly the 'essential' amino acids (Dent and Walshe, 1954), These are certainly present in the urine of our cases, but not in gross excess compared to other amino acids. It would also be difficult to explain why the effect of amino acid leak is greatest upon the mechanisms for phosphate reabsorption and ammonia formation, whilst other electrolytes and water continue to be reabsorbed normally. The question of aetiology must therefore be considered an open one.

It should also be noted that a phosphate leak and radiological rickets do not run *pari passu*, and in fact the phosphate leak may precede the rickets by a matter of years. Thus the larger twin, Glynis, was shown to have a low blood phosphorus level and a diminished tubular phosphate reabsorption in January, 1958 and it is not possible to say how long before that they had been abnormal; however, no rickets was present, nor has it developed since. Again, one of the Great Ormond Street cases, noted previously, was found to have a low serum phosphorus level (2·7 mg./100 ml.) at the age of 1½ years, but she remained free of rickets until she was 4½ years old. During this period the serum alkaline phosphatase level remained normal. The reason for the delayed appearance of rickets is not clear, but may depend first on the degree of phosphate leak, and secondly, as in the development of true renal rickets, on the rate of growth of bone, being more likely at times of rapid growth. This, in turn, will depend on many other factors apart from tubular leaks.

Nevertheless, apart from the larger twin mentioned in this paper, we know of no other case in which a tubular phosphate leak, once demonstrated in a child, has not been followed in a shorter or longer time by rickets and it should, therefore, be regarded as a definite warning. We are less certain of the value of the serum alkaline phosphatase in this connexion. Several of the Great Ormond Street cases already quoted (including the child mentioned above) had normal phosphatase levels during the period preceding and even during the development of rickets. In most of the cases, however, the level was elevated and remained so even after the rickets was healed. It seems, therefore, that in children with a tubular absorption defect for phosphorus, the serum alkaline phosphatase is a poor guide of the imminence of rickets, and also of its cure under vitamin D therapy. This

is in contrast to the situation in vitamin D deficiency rickets, in which a rise of serum alkaline phosphatase is an early and certain diagnostic indication, and an early fall of serum alkaline phosphatase a good indication of cure.

The treatment used in our cases was influenced by a report by Fraser, Jaco, Yendt, Munn and Liu (1957) that healing of vitamin D-resistant rickets could be demonstrated within a few days of setting up a continuous intravenous infusion of an isotonic sodium phosphate solution at a rate sufficient to maintain the serum inorganic phosphorus level above 5 mg./100 ml., without recourse to vitamin D therapy. A reversion to active rickets took place when the infusion was discontinued. The beneficial effect of this experimental therapy was due to a temporary restoration of the serum phosphorus to a normal level. Theoretically, if sufficient phosphorus could be fed by mouth and absorbed to achieve a normal serum phosphorus level, a comparable benefit to the rachitic process should be achieved, although against a background of renal tubular wastage of phosphorus, this possibility seemed remote. This has unfortunately proved to be the case. The smaller twin, Lindsay, began to heal her rickets on vitamin D alone and this process continued after she began her oral phosphate solution. In spite of this healing, however, her serum phosphorus level remained abnormally low. After the phosphate solution was discontinued in October, 1958, her rickets has remained healed under the influence of a large dose of vitamin D and her serum phosphorus level is unchanged.

Glynis was started on the oral phosphate solution alone, without vitamin D, as a prophylactic measure after a tubular phosphate leak and a raised serum alkaline phosphatase level had been demonstrated. It was hoped at that time to gauge the effect of the treatment by the alkaline phosphatase level, but we now realize that in the type of endogenous rickets with which we were dealing the phosphatase level is of much less value for this purpose than it is in vitamin D deficiency rickets. Her serum phosphorus and alkaline phosphatase levels did not alter materially during this treatment or during subsequent treatment with vitamin D alone.

Though neither case was a wholly clear-cut experiment, we have concluded that oral phosphate solutions in the doses used were without effect, and that the healing of rickets in the rachitic twin was due to the influence of vitamin D alone.

This family also demonstrates another point of unique interest, namely the dominant inheritance of this multiple renal tubular defect. Most other renal tubular defects are inherited by recessive, incomplete recessive or sex-linked mechanisms and the only other example of a tubular defect inherited by dominant autosomal means is renal glycosuria.

Summary

The development of a renal tubular phosphate leak and an acidosis is described in twins who were reported in 1955 to leak glucose and amino acids only.

The possible aetiology of these fresh tubular disturbances is discussed. The consequent rickets in one twin has healed under treatment with large doses of vitamin D, while oral phosphate solution has been ineffective. The dominant mode of inheritance of this condition is most unusual.

We wish to record our thanks to Professor C. H. Gray and Professor C. E. Dent for their help and advice; to Dr. M. Rinsler for estimating the phosphorus Tm; and to Dr. F. V. Flynn for the electrophoretic study of the urinary protein.

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CEREBELLAR HYPOPLASIA IN WERDNIG-HOFFMANN DISEASE

BY

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It is well established that the neuropathological changes in the Werdnig-Hoffmann disease are not confined to the spinal cord and brain stem, and that sensory as well as motor nuclei may be involved. Gruner and Bargeton (1952) found evidence of neuronal degeneration in the thalamus in all their nine cases and Radermecker (1951, 1953) has reported occasional lesions in the striatum, globus pallidus, nucleus subthalamicus, cerebellar cortex and dentate nucleus. In contrast to this wealth of degenerative change, reports of malformations in association with Werdnig-Hoffmann disease have been conspicuous by their absence, except for doubling of the central canal of the spinal cord in one of Werdnig's (1891) cases, and a few reports of minor neuronal heterotopias (Brandt, 1950). There is, however, an account by Radermecker and Liessens (1954) of a family in which the same sibship contained proved cases of Werdnig-Hoffmann disease and also a child who suffered from a non-progressive ataxia considered to be due to cerebellar hypoplasia.

The case to be described in this paper is remarkable not only for the presence of a prenatal cerebellar malformation but also for the widespread distribution of supra-segmental degenerative lesions. Evidence will be adduced to support the view that in Werdnig-Hoffmann disease, as in certain other infantile encephalopathies, malformation may be an early expression of the genetic abnormality responsible for the later manifestations of the disease.

Case Report

Clinical History. J.S., a boy, was the only child of healthy parents who were not blood relatives. The pregnancy had been uneventful. He was born by breech presentation and sustained a fracture of the right humerus with a right Erb's palsy. The birth weight was 4¾ lb. There was initial difficulty in establishing respiration and he was extremely limp and had to be tube fed. After the first three weeks he began to feed and the limpness became less noticeable. At about the age of 2 months a slight adductor spasm of the legs was observed and as time passed it was noted that he was not only failing to reach the normal milestones of development but that a progressive mental deterioration was taking place. Death occurred from bronchopneumonia at the age of 6 months.

Examination of the Central Nervous System.

MACROSCOPIC. The brain after fixation weighed 603 g. of which the cerebellum and brain stem accounted for 21 g. The convolutional pattern of the cerebral hemispheres was normal. On coronal section it was seen that the corpus callosum was thin, and its splenium unduly small, that the lateral ventricles were moderately enlarged, and that the thalami appeared to be unusually small. The cerebellum was small and flat and its posterior margin only reached a point 4 cm. from the occipital poles. This reduction in size affected the inferior semilunar lobules, the tonsils and biventral lobules, the gyri of which were unusually broad and separated from each other by very shallow sulci. This foetal type of configuration was symmetrical (Fig. 1). The inferior vermis did not share in this change, nor did the flocculi. The dorsal surface of the cerebellum was normally convoluted.

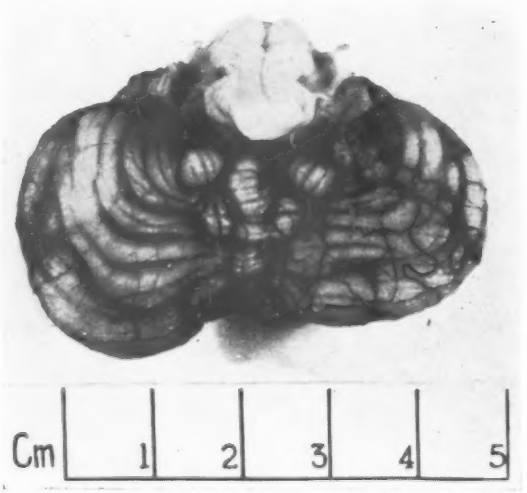


FIG. 1.—Cerebellum; inferior surface showing primitive simplification of gyri.

MICROSCOPIC. Whole-brain coronal celloidin sections were prepared serially from the anterior part of the corpus striatum to the pulvinar, every 80th section being stained for nerve cells and the adjoining section for myelin. The occipital lobes were examined separately. The cerebellum and brain stem were also serially sectioned in a plane at right angles to the axis of the brain stem, every 40th section being examined. Representative sections were stained for fibrous neuroglia by the Holzer method and for axis cylinders by the Gros-Bielschowsky stain. The spinal cord was examined both in celloidin and frozen sections.

SPINAL CORD. There was a marked reduction in the number of anterior horn cells in the cervical and lumbar regions. Several of the remaining nerve cells showed swelling and chromatolysis, the nucleus often lying flattened at the margin of the cell (Fig. 2). In the grey matter there was a diffuse overgrowth of fibrillary neuroglia, fanning out into the anterior and lateral columns in the cervical and lumbar segments and also involving the posterior columns in the thoracic region. This gliosis did not reach the periphery of the cord (Fig. 3). Myelination of the tracts was within normal limits except in the thoracic and lumbar regions where there was a clear-cut pallor in the crossed pyramidal tracts (Fig. 4). In the lumbar cord the well myelinated posterior columns showed conspicuous fibrillary gliosis. The anterior nerve roots were atrophic in the cervical and lumbar enlargements.

BRAIN STEM. Examination of the serial sections provided evidence of widespread neuronal degeneration, though myelination was normal for the patient's age. Swollen chromatolytic nerve cells with eccentric nuclei were found in the following cranial nerve motor nuclei: XII, VII, VI, V, IV and III (Fig. 6b). The hypoglossal nucleus at some levels also showed a reduction in the number of nerve cells. The most caudal part of the inferior olives contained few nerve cells and the capsule

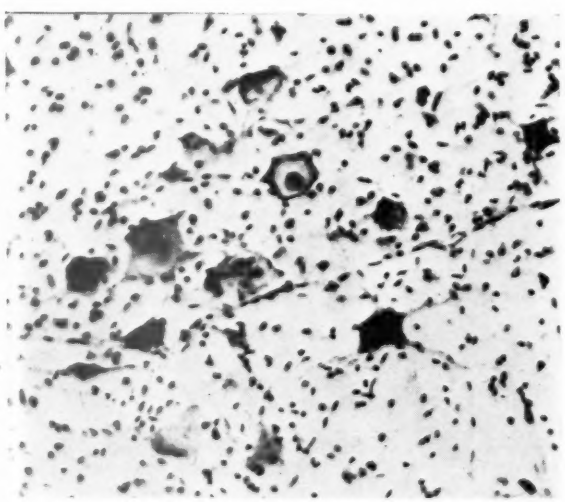


FIG. 2.—Spinal cord; lumbar enlargement; the anterior horn cells show various stages of degeneration. (Carbol azure × 170.)

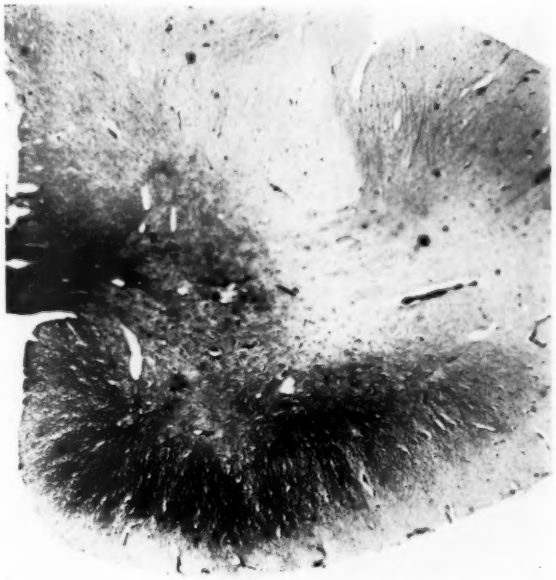


FIG. 3.—Cervical cord; fibrous gliosis in the anterior columns. (Holzer × 18.)

and hilum showed heavy fibrillary gliosis. The dorsal accessory olive was also partially degenerated. In places the oral parts of the inferior olives were poorly convoluted, the dorsal band being formed by a widely spaced double line of nerve cells. There was severe degeneration and gliosis of the medial and lateral vestibular nuclei in which neuronophagia was in progress (Fig. 5). In the oral part of the pons the nuclei pontis showed a marked reduction in the nerve cell population of the dorso-lateral cell groups. There was marked fibrous gliosis in the transverse fibres of the pons, but no demonstrable reduction in the numbers of axons. A large nest of primitive nerve cells was attached to the posterior medullary velum and bulged conspicuously into the fourth ventricle (Fig. 10).

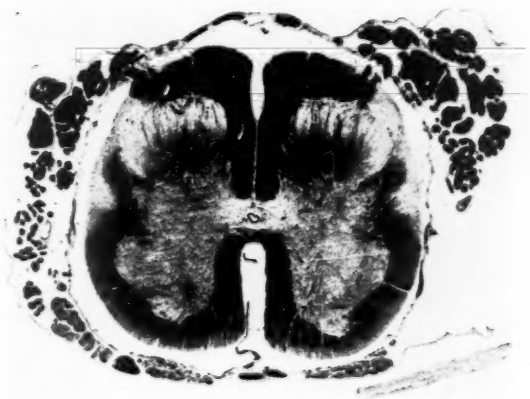
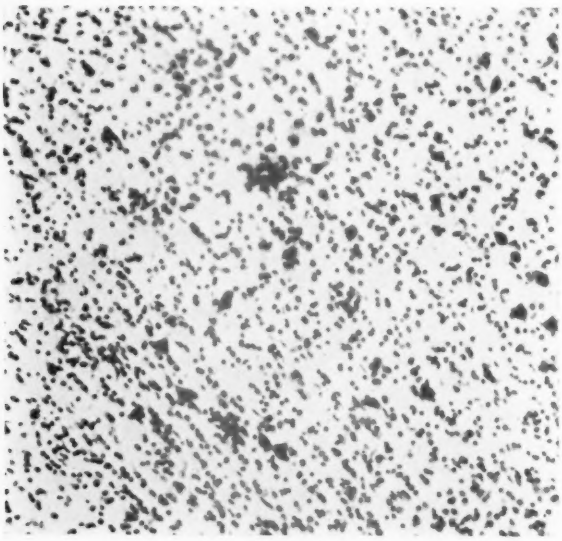


FIG. 4.—Fifth lumbar segment; atrophy of the anterior roots. The lateral pyramidal tracts are demyelinated. (Heidenhain × 8.)



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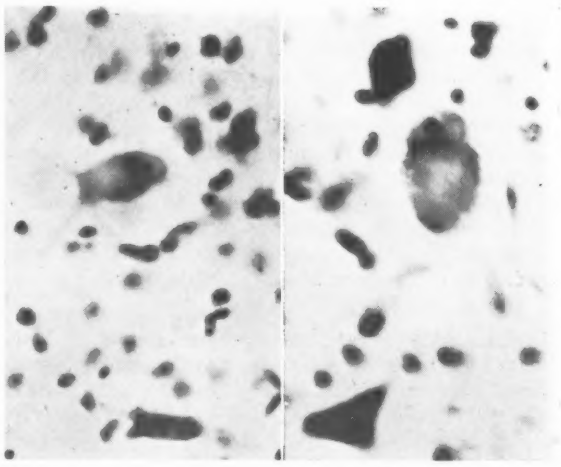

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FIG. 6.

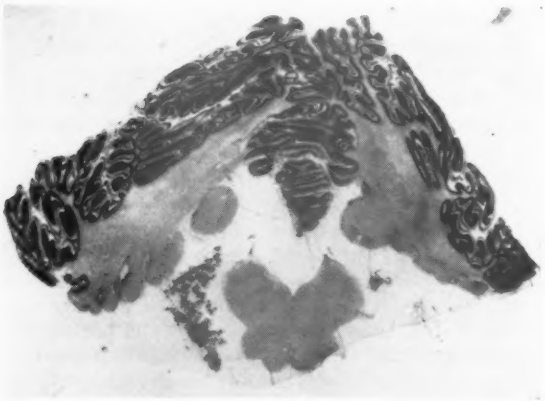

FIG. 7.

FIG. 9.

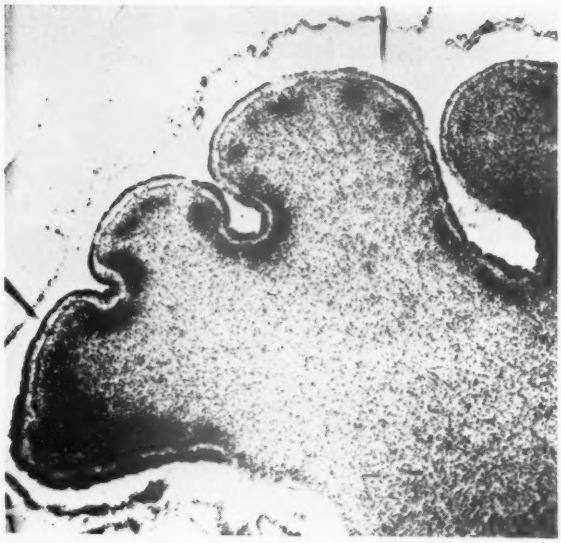

FIG. 8.

FIG. 5.—Lateral vestibular nucleus showing gliosis, loss of many nerve cells and two figures of neuronophagia. (Carbol azure × 120.)

FIG. 6.—Typical chromatolytic nerve cell of globus pallidus (a) and of trochlear nucleus (b). (Carbol azure (a) × 375; (b) × 470.)

FIG. 7.—Atrophy of the gyri of the tonsils and inferior semilunar lobules. The vermis and dorsal parts of the lateral lobes are hypoplastic. (Carbol azure × 1·5.)

FIG. 8.—Atrophic gyri showing patchy remnants of the internal granular layer. (Carbol azure × 17.)

FIG. 9.—Demyelination of the dentate nuclei and their hila. (Heidenhain × 2·7.)

CEREBELLUM. Microscopic examination of the poorly developed gyri of the inferior surface showed that most of these formations were devoid of nerve cells and axis cylinders (Fig. 7). In areas adjoining the more normal cortex the internal granular layer was represented by small groups of cells usually in the deeper parts of the walls of the shallow sulci (Fig. 8). In such areas a few Purkinje cells were seen, some of which were binucleate, and a thin external granular layer, less dense than elsewhere in the cerebellum, was also present. These atrophic gyri were filled by a thin, uniform feltwork of glial fibres except in the molecular layer where the fibres of the Bergmann astrocytes formed a dense brushwork.

The folia of the vermis and dorsal parts of the lateral lobes were normally constituted and there was no sign of neuronal degeneration. Myelination was unimpaired though a mild fibrous gliosis was present throughout the central white matter. Both dentate nuclei showed a severe and diffuse loss of nerve cells accompanied by demyelination and heavy gliosis of their hila (Figs. 9 and 10). The caudal part of both nuclei had not developed their normal convoluted pattern and appeared to have been formed by rounded masses of nerve cells. The nucleus fastigii was intact.

FIG. 10.—Fibrous gliosis of the dentate nuclei and deeper white matter of the cerebellar hemispheres. The pons shows gliosis of the nuclei in the floor of the fourth ventricle and in the pes pontis. The outline of the large nest of primitive cells is seen in the roof of the ventricle. (Holzer × 2·7.)

BASAL GANGLIA. Widespread and remarkably symmetrical loss of nerve cells was found in the thalamus, the severest changes being present in the postero-lateral group of nuclei and in the central part of the dorso-medial nucleus (Fig. 11). Many of the surviving nerve

FIG. 11.—Left thalamus showing extensive loss of nerve cells in the anterior, medial and lateral nuclei. (Carbol azure × 8.)

cells showed complete chromatolysis with lateral displacement of the nucleus, and microglial activity was often conspicuous in the neighbourhood of such cells. The nuclei of the midline, and the centro-median and parafascicular nuclei were preserved. The external geniculate body also contained scattered chromatolytic cells. No pathological changes were present in the caudate nucleus or putamen of either side. The globus

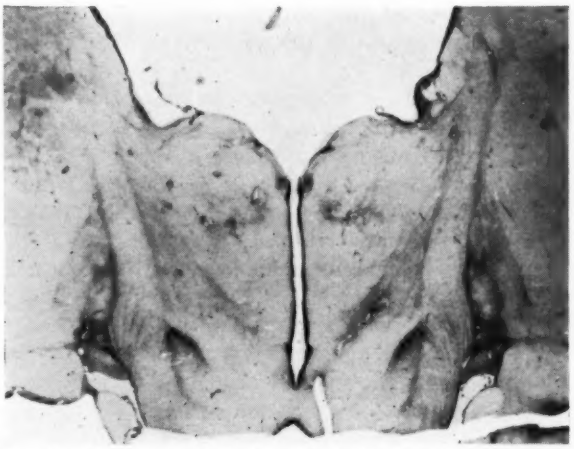

FIG. 12.—Fibrous gliosis marks each globus pallidus and nucleus subthalamicus, Slight gliosis is also seen in the thalami. (Holzer × 2·7.)

pallidus was feebly myelinated and showed diffuse fibrous gliosis which was most marked in the medullary laminae. There was a patchy loss of nerve cells, many of the remaining cells staining feebly and a few being fully chromatolytic. The corpora Luysii showed a symmetrical atrophy of the dorso-lateral half, there being a severe loss of nerve cells and marked fibrous gliosis. Here also there were occasional chromatolytic cells and patchy microglial activity.

CEREBRAL CORTEX. A wide sampling revealed no pathological changes. The white matter of the centrum ovale, gyral cores and long tracts coloured less intensely with the myelin stain than is usual at 6 months, but no gliosis was present.

Discussion

The progressive neurological deterioration noted in this child had struck a discordant note in a history otherwise suggestive of cerebral birth trauma, and the neuropathological examination revealed the classical features of Werdnig-Hoffmann disease in the spinal cord and brain stem, while showing no evidence of vascular or anoxic lesions. The chromatolytic swelling of the anterior horn cells and of the neurones in the cranial nerve nuclei closely resembled that of axonal reaction and is highly characteristic of Werdnig-Hoffmann disease. On the other hand, partial degeneration of the pyramidal tracts has been reported only in a minority of cases (Radermecker, 1951). In the present instance this lesion may well have been responsible for the adductor spasticity observed at one stage of the illness.

The loss of nerve cells in the thalami and pallido-Luysial system was exceptionally severe, but the presence of microglial activity and the typical chromatolysis in some of the remaining nerve cells were again features of Werdnig-Hoffmann disease that have been described in several other cases, including two of my own in which there was also widespread neuronal devastation in the thalami (Norman, 1958).

The peculiar combination of cerebellar hypoplasia and convolutional atrophy is a unique finding in Werdnig-Hoffmann disease. Although it is well established that the disease may be present at birth (Beevor, 1902), up to now there has been no evidence that the degenerative process may start so early in foetal life as to interfere with normal structural development. Yet in the present case the primitive form of the gyri in the ventral parts of the lateral lobes taken in conjunction with the marked gliosis and lack of cortical neurones leaves little doubt as to the prenatal onset of the abiotrophy. The minor malformations noted in the partially degenerate dentate nuclei and inferior olives also point to the same conclusion.

Cerebellar hypoplasia has been found associated with progressive neuronal degeneration in the brain stem and basal ganglia in other infantile encephalopathies (Gross and Kaltenbäck, 1959; Norman and Urich, 1958) and there is reason to believe that the two processes are not fortuitously linked. The appearance of cerebellar hypoplasia in a case of Werdnig-Hoffmann disease thus strengthens the theory that both the malformation and abiotrophy may be the expression of a single genetic abnormality. There is some clinical evidence to support this view. Radermecker and Liessens (1954) reported a remarkable pedigree of two interrelated Flemish families in which four infants suffered from Werdnig-Hoffmann disease. Another sibling presented signs of cerebellar ataxia at the end of the second year of life. In this patient the muscles were poorly developed but their electrical reactions were normal. By the age of 5 years this child had shown an improvement both in the ataxia and in his muscular development and there was still no sign of motor neurone disease. The diagnosis of cerebellar hypoplasia was made. The authors hesitated to classify this non-progressive cerebellar syndrome as a forme fruste of Werdnig-Hoffmann disease, but in the light of the present case this explanation may well be correct.

Summary

Neuropathological examination of a 6-month-old infant revealed the usual features of Werdnig-Hoffmann disease in the spinal cord and brain stem. There was widespread degeneration of nerve cells in the thalami, and symmetrical pallido-Luysial atrophy. The cerebellum was hypoplastic and in the ventral parts of the lateral lobes the convolutions were stunted in development and showed atrophic changes. Severe degeneration had taken place in both dentate nuclei and was accompanied by dense fibrillary gliosis and an almost complete loss of myelinated fibres in the hila. Reference is made to other forms of infantile encephalopathy in which cerebellar hypoplasia has been found in association with progressive neuronal degeneration elsewhere in the brain. The findings in the present case support the theory that, in certain instances, prenatal malformation and abiotrophy are expressions of the same genetic abnormality.

I am greatly indebted to Dr. W. J. Matheson for the use of his clinical notes and to Dr. E. M. Stirk who performed the autopsy and made this brain available for examination.

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DIFFUSE PROGRESSIVE INTERSTITIAL FIBROSIS OF THE LUNGS IN CHILDHOOD (HAMMAN-RICH SYNDROME)

BY

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Hamman and Rich (1935) briefly described four cases of bilateral diffuse interstitial fibrosis of the lungs of unknown aetiology. In 1944, they described this condition in detail under the title 'Acute diffuse interstitial fibrosis of the lungs' (Hamman and Rich, 1944).

Since then the condition has become known as the 'Hamman-Rich syndrome' but is now perhaps more correctly referred to as 'Diffuse progressive interstitial fibrosis of the lungs' (Beams and Harmos, 1949).

Grant, Hillis and Davidson (1956) collected 36 cases from the literature and added three of their own. Rubin and Lubliner (1957) recognized 39 recorded cases and added 15 of their own. Since then sporadic reports of cases have appeared, and Scadding (1960) added 26 cases to the literature. The majority of reported cases have been in adults; in childhood the disease is rare, only six cases having been previously recorded.

The first report of the condition occurring in a child was by Bradley (1956). He described the clinical and autopsy findings in a 9-year-old girl. Since that time the following cases have been reported: Baar and Braid (1957) described the case of a 3-year-old boy; Feinerman and Harris (1957) of a 7-month-old girl and an 8-year-old boy; Diamond (1958) of a 4-year-old Negro boy who, in addition, had stenosis of the right pulmonary artery and complete occlusion of the right pulmonary vein, and Mann (1959) an 8-month-old girl.

Wilson and Mikity (1960) have recently reported a syndrome resembling the Hamman-Rich syndrome which occurs in premature babies. They gave details of five infants, two of whom had pulmonary signs and symptoms suggestive of the Hamman-Rich syndrome. It is not certain, however, that these should be regarded as proved cases.

Case 1: J.L.

John was the second child of healthy parents. He was born after a normal pregnancy and labour (birth weight 7 lb. 4 oz.). He developed normally for the first three months of life and reached a weight of 11 lb. 10 oz. He then developed, over the course of a week, a slight fever, cough and 'stuffy' nose.

On admission to the Sheffield Children's Hospital, under the care of Professor Illingworth, he was slightly cyanosed. His temperature was 100° F., his heart rate 180 per minute and his respiratory rate 30 per minute. A grade 3/6 systolic murmur was audible over the precordium, and both liver and spleen were palpable two fingers' breath below the costal margin. Investigations showed nothing abnormal apart from the chest radiograph, which revealed bronchopneumonic changes throughout both lung fields. He was treated with oxygen, penicillin and digoxin and seemed to improve. His liver became less easily palpable and the systolic murmur disappeared.

He was discharged home, but four days later was readmitted with marked cyanosis which disappeared when he was placed in an oxygen tent. The systolic murmur had returned and he was dyspnoeic, but had no fever. The liver was not so large, but the chest radiograph showed the same changes as previously.

During the next three months the child's condition steadily deteriorated. He became a blue-grey colour when not receiving oxygen, lost weight and his haemoglobin level rose from 12·1 g. % on his first admission to 14·4 g. % just before death. It was thought that he probably had a congenital heart lesion with cardiac failure. The electrocardiogram showed evidence of right ventricular diastolic overloading, but a cine-angiocardiogram was normal. Repeated blood cultures were negative. He was treated with tetracycline on four occasions, penicillin twice, chloramphenicol once, and was also given digoxin, triamcinolone and nystatin for persistent oral thrush. No therapy except oxygen appeared to help him. All investigations remained negative, but the chest radiograph showed an increasing haziness of the whole lung field with an almost ground-glass appearance (Fig. 1). He died at the age of 6½ months.

Necropsy. The body was that of an extremely wasted male infant weighing 3,097g. Scattered petechial haemorrhages were present over the face, abdomen and ankles, and fading petechial haemorrhages were present in both groins.

RESPIRATORY TRACT. Lesions of thrush were present in the mouth and pharynx. The trachea and main bronchi appeared to be normal.

Both lungs were bulky and voluminous and filled the thoracic cavity. There were depressions on the posterior surface of both lungs which corresponded with the posterior aspect of the ribs. These depressions had apparently been produced by pressure of the lungs against the thoracic cage. All lobes of both lungs were firm and gave the appearance of consolidation, but there was no congestion or oedema. The smaller bronchi and bronchioles appeared normal and contained no exudate. The pleural surface of both lungs showed some dilatation of vessels. The cut surface of the lungs had a mottled appearance, consisting of reddish and whitish areas, and also showed a diffuse lace-like pattern of firm whitish fibrous tissue (Fig. 2). The tracheo-bronchial and some of the mediastinal lymph nodes were slightly enlarged, a little congested and soft, but there was no evidence of caseation or calcification.

CARDIOVASCULAR SYSTEM. There was moderate distension of the jugular veins and a distended azygos vein was present. The heart appeared to be normally developed. There was no congenital abnormality and no evidence of right ventricular hypertrophy.

The liver was slightly enlarged and congested.

The brain showed engorgement of the cerebral veins.

All other organs appeared normal.

Histological Findings. The following appearances were found in approximately equal severity in all lobes of both lungs: there was a great increase in the thickness of the alveolar wall, apparently due to a combination of oedema and increase in argentaffine fibres. Large mononuclear cells and a few lymphocytes were present in the interstitial tissue but polymorphonuclear leucocytes and eosinophil leucocytes were scanty. There was marked vascularity of the interstitial tissue. Many alveoli were dilated and the alveolar epithelium was replaced by increased amounts of connective tissue which produced a 'pseudo-hyaline membrane' appearance. Many other alveoli were not dilated but were small and lined by cuboidal epithelium. Alveoli, alveolar ducts, bronchioli and bronchi were either empty or contained a few mononuclear cells which appeared to be swollen alveolar epithelial cells which had become separated from the alveolar wall. No evidence of fungal infection was seen.

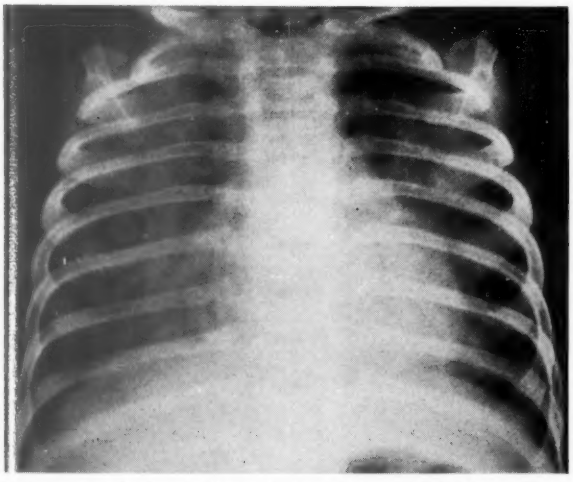

FIG. 1.—Case 1, chest radiograph showing 'ground glass' appearance of lung fields.

FIG. 2.—Case 1, cut surface of lung showing mottled appearance.

Case 2: A.R.

Angela was the third child of healthy parents (birth weight 6 lb.). She had been perfectly well until she was vaccinated against smallpox at the age of 14 weeks. She had a strong reaction to the vaccination and the scab had still not separated five weeks later. Three days after the vaccination she began to vomit and had a bout of diarrhoea which lasted five days. Four days after the vaccination she started to cough and this persisted. At that time she showed no evidence of cyanosis. During the next four weeks the cough became worse. The child refused feeds, vomited occasionally and then became cyanosed.

When seen by Dr. L. A. Hawkins at the Doncaster Royal Infirmary, Angela was 18 weeks old. She was a greyish blue colour with a respiration rate of 60 per minute. There was no evidence of respiratory obstruction. Widespread crepitations were audible. The pulse rate was uncountable. No abnormality was noted in the heart. The temperature was 101° F.

On admission she was put into an oxygen tent and her colour rapidly became normal. This rapid improvement in response to oxygen continued until just before her death and was a notable feature of the case. Apart from oxygen, Angela was treated with penicillin (two courses), chloramphenicol, tetracycline, chlortetracycline and streptomycin but without any improvement. Radiological examination showed a widespread, mottled opacity of both lung fields, so much so that almost no normal lung translucency could be seen. It was difficult to distinguish the heart from the lungs and no abnormality of the heart was observed.

Angela's condition deteriorated and she died at the age of 7 months, 10 weeks after the onset of her illness.

Necropsy. The lungs were voluminous and on the posterior aspects, slight markings were present which corresponded to the posterior part of the ribs. The lungs were firm and on cut section showed a fleshy appearance with a variegated pattern of pale and reddish areas. No definite consolidation was present and no frank pus was seen.

Histological Findings. All lobes of both lungs showed a similar appearance. There was gross thickening of the alveolar walls which appeared to be due to a combination of increased connective tissue, oedema and cellular infiltrate of mononuclear cells and occasional eosinophil leucocytes. Dilated capillaries were present in the interstitial tissue. The majority of alveoli were lined by cuboidal epithelium; other alveoli were distended. The smaller bronchi, bronchioles and alveoli were either empty or contained swollen mononuclear cells which appeared to have been derived from the alveolar epithelium. The heart showed no gross abnormality and the other organs were normal.

Case 3: L.S.

Linda was well until the age of 13 months when she developed a respiratory tract infection with otitis media and a cough. The otitis improved after two weeks, but the cough became progressively worse and the respiratory rate became rapid. She was admitted to the Sheffield Children's Hospital under the care of Professor Illingworth.

On examination she was a pale, coughing baby with a tinge of cyanosis. The temperature was 100° F., and the respiratory rate about 80 per minute. On auscultation of her chest, crepitations were heard all over both lung fields. A radiograph showed emphysematous lung fields with patchy consolidation and one possible cavity in the right mid-zone. The pulmonary artery was prominent.

Linda was put into an oxygen tent and treated with tetracycline. Her haemoglobin was 12·9 g. % and her total leucocyte count 21,000, 68% of which were neutrophils. Gastric washings on admission showed no pathogenic organisms.

There was a slight initial improvement, but after the first two weeks she began to deteriorate. She became very cyanosed when out of oxygen, but was comparatively cheerful in the oxygen tent. The pulmonary crepitations were always audible, although her cough became less troublesome. Serial radiographs showed increasing emphysema with areas of consolidation uniformly distributed throughout both lung fields (Fig. 3). No abscess cavities were seen. Her heart enlarged progressively, especially the right ventricle, and the pulmonary artery became very prominent. Her haemoglobin rose, until just before death it was 16·7 g. %. *Staphylococcus aureus* coagulase positive was grown from cough swabs on eight occasions in specimens taken at aproxpimately monthly intervals.

Linda was treated with courses of penicillin, chlortetracycline, oxytetracycline, sulphadimidine, chloramphenicol and erythromycin. She was also given cortisone for two months and, when she was in heart failure, digoxin. No treatment, apart from oxygen, made any difference to her general condition or altered the persistent growth of *Staphylococcus aureus* in her sputum, even though *in vitro* studies showed that the organisms remained fully sensitive to chloramphenicol and erythromycin throughout.

Linda developed progressive cor pulmonale as shown by chest radiographs and electrocardiograms, and she died in heart failure eight months after the initial appearance of her symptoms.

Necropsy. The body was that of a wasted female child, the sternum was prominent and the antero-posterior diameter of the chest was increased.

RESPIRATORY TRACT. The larynx, pharynx, trachea and larger bronchi appeared normal.

The lungs were slightly more bulky than normal and the pleural surface showed irregularity due to the presence of small sub-pleural cysts which varied in size from 1 mm. to 1 cm. in diameter. The pleural surface showed mottled areas of red congested tissue and white depressed areas due to fibrous tissue. On cut section the mottled appearance was seen to be present throughout all lobes of both lungs.

CARDIOVASCULAR SYSTEM. The heart was increased in size due to right ventricular hypertrophy. There was no evidence of congenital heart disease. The pulmonary artery appeared slightly increased in thickness. There was distension of the jugular veins.

The liver was enlarged and congested. The thymus showed marked involution. All other organs were normal.

Histological Findings. Throughout all lobes of both lungs, there was an increase in thickness of the alveolar

FIG. 3.—Case 3, chest radiograph showing areas of consolidation, enlargement of the heart and prominent pulmonary artery.

valls. This was due to increased amounts of connective issue and collections of cells which included macro-)hages, fibroblasts, plasma cells and some eosinophils. Many alveoli appeared small or normal in size and were lined by cuboidal epithelium (Fig. 4). Other alveoli were dilated and cysts were present which were lined in some areas by a thin layer of fibrous tissue, and in other areas by ciliated columnar epithelium.

The heart showed slight hypertrophy of muscle fibres in the right ventricle. There was no evidence of myocarditis.

The pulmonary artery showed some sub-intimal thickening. The thymus showed gross involution. The liver showed congestion and fatty degeneration. The spleen was congested but was otherwise normal.

Discussion

An analysis of the six previously recorded childhood cases (excluding the five premature babies) in conjunction with our own three cases, enables a composite picture of the syndrome to be given. The sex incidence is approximately equal (four boys and five girls). The ages at onset were: 3 months (two cases), 4 months (two cases), 5 months (two cases), 13 months, 2 years 5 months and 6 years 9 months. Five cases survived six months or less, while three cases survived between eight months and three and a half years. One 8-year-old boy was still alive at the time his case history was published one year after the onset of the disease.

Five cases began with an upper respiratory tract infection. Two cases began with fever and respiratory tract symptoms. One case apparently followed whooping cough and one case followed vaccination against smallpox. The usual story was of cough, dyspnoea and cyanosis persisting after an infection had apparently abated. The cyanosis was relieved by oxygen. Several authors remarked on the remarkable absence of signs in the chest, but some of the children were seen months after the commencement of the disease. On the other hand a few cases had persistent crepitations throughout the illness.

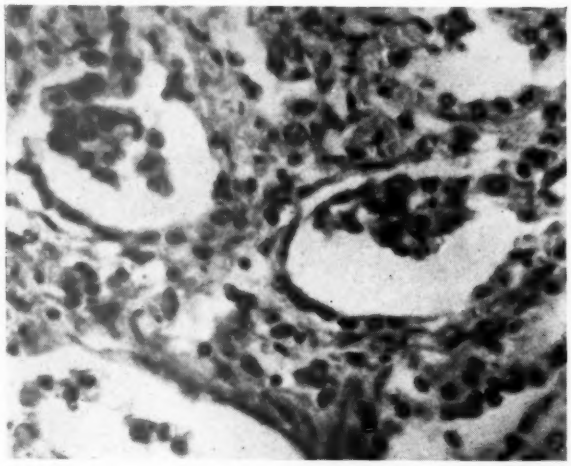

FIG. 4.—Case 3, lung section showing broadening of interalveolar interstitial tissue and cuboidal epithelium lining the alveoli. (H. and E. × 295.)

Six out of seven cases died in heart failure. In the child who was still alive, the cardiac second sound was reported as being very loud and split. In one case report the heart was not mentioned.

In our first child the presence of a systolic murmur which was shown to be presystolic on a phonocardiogram, coupled with dilatation of the pulmonary artery on a radiograph, right ventricular overloading on the electrocardiogram and clinical evidence of right-sided heart failure, suggested the diagnosis of a congenital heart lesion. An angiocardiogram, however, was normal. A similar case was reported by Bradley (1956); the child had a loud systolic and later diastolic murmur and cardiac catheterization was performed. A general increase of pressures in the right side of the heart was found (figures not given), but no other abnormality was discovered. At autopsy no congenital heart lesion was found.

The radiological appearance of the nine cases varied. Two cases showed patchy consolidation and emphysema, five cases showed diffuse infiltration, and two cases showed a ground glass haziness of the lung fields. The abnormal appearance was often more marked on one side than the other.

In our third case the diagnosis of staphylococcal pneumonia either with or without fibrocystic disease of the pancreas was seriously considered. This was because of the radiological appearance of patchy consolidation and possible pneumatoceles, and also because of the constant finding of haemolytic staphylococci in the sputum.

Diffuse progressive interstitial fibrosis of the lungs is a clinical syndrome which should be considered in any child with persistent dyspnoea, tachypnoea, cyanosis improved by oxygen, and heart failure. The most important differential diagnosis is congenital heart disease.

Aetiology. Various possibilities have been suggested as aetiological factors in cases of 'idiopathic' diffuse interstitial pulmonary fibrosis. These include a reaction to some form of chemical irritant, the result of a viral infection or infection with pleuropneumonia-like organisms or an incompletely resolved pneumonia. A relationship with the collagen disease has also been suggested, and cases

of rheumatoid arthritis with progressive pulmonary fibrosis have been recorded in adults (Rubin and Lubliner, 1957).

The concept that auto immunity may be concerned has received some support from Read (1958a and 1958b) who prepared, in rabbits, an anti-rat lung serum which, when administered to rats, resulted in interstitial fibrosis of the rat lung.

Pathology. The naked eye appearances of the lung in all our three cases showed a similar appearance. The lungs were voluminous and increased in bulk. They were uniformly firm in consistence and the cut surface showed a variegated pattern of greyish white and pale reddish areas. In two cases there were prominent dilated blood vessels present on the pleural surface. In one case, the presence of small cysts was noted.

Histological Findings. The histopathological findings in our three cases fulfilled the criteria described by Hamman and Rich. The main pathological feature was broadening of the interstitial tissue of interalveolar septa. This pathological change involved all lobes of both lungs. The broadening of interstitial tissue was due to oedema, increased numbers of argentaffine and collagenous fibres and cellular infiltration. The cellular infiltrate comprised large mononuclear cells, lymphocytes, plasma cells and eosinophil leucocytes in varying proportions in the three cases.

In Case 3 of our series frequent isolation of haemolytic *Staphylococcus aureus* from the sputum, together with the cystic changes in the lungs, was suggestive of staphylococcal pneumonia. In organizing pneumonia, however, changes are usually lobar or lobular and not diffuse and even if both lungs were involved uniformly, the alveoli themselves are filled with organized exudate. In this case there was no organized alveolar exudate, no evidence of suppuration and the walls of the cyst were lined by a thin layer of fibrous tissue and in some parts respiratory epithelium. The cysts were probably produced by dilatation of bronchioles and there was no evidence of a surrounding inflammatory reaction.

Summary

Three cases of the Hamman-Rich syndrome in childhood are described. The ages of the children at death were 6½, 7 and 23 months.

These cases were manifested clinically by dyspnoea, tachypnoea and cyanosis. The respiratory symptoms became steadily more marked and two of the children died with right-sided cardiac failure.

The pathological findings in the lungs were similar in all three cases, the main macroscopic appearances consisting of increase in bulk of the lungs with evidence of fibrosis, and the main histological feature being broadening of the interalveolar interstitial tissue.

No treatment was of any avail apart from oxygen.

The Hamman-Rich syndrome should be considered in any child who has persistent cough, dyspnoea, tachypnoea, cyanosis improved by oxygen, and heart failure.

We would like to thank Professor R. S. Illingworth, under whom two of these cases were admitted, and Dr. J. L. Emery for kindly criticizing this paper. Dr. L. A. Hawkins kindly supplied us with the clinical details of Case 2.

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INTRACRANIAL COMPLICATIONS OF LEUKAEMIA TREATED WITH INTRATHECAL AMETHOPTERIN*

BY

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Because the peripheral blood and bone marrow in acute leukaemia of childhood can be controlled temporarily by the anti-folic acid, the anti-purine and the steroid drugs, the prognosis of the disease has improved. However, none of these drugs prevents leukaemic infiltration of the brain, meninges or cranial nerves. Whiteside, Philips, Dargeon and Burchenal (1958) demonstrated that this was probably because an orally or parenterally administered drug did not penetrate the blood cerebrospinal fluid (C.S.F.) barrier in sufficient concentration to give a therapeutic level. However, when the anti-folic acid drug, amethopterin (4-amino-N10 methyl pteroylglutamic acid) was given intrathecally, the C.S.F. levels were 30 to 100 times higher than those found after a massive single oral dose.

Treatment of these neurological complications of leukaemia with intrathecal amethopterin have been published in the American literature (Whiteside *et al.*, 1958; Cramblett, 1959; Murphy, 1959). In the first child reported here the response to intrathecal therapy was quite dramatic. The report of a second child who had mild meningeal involvement is included because both this and the first child had swellings on the skull surface which were presumed to be leukaemic deposits and which disappeared after treatment. The report is intended primarily to stress the treatment of the intracranial complications of leukaemia, so that only brief reference is made to the general aspects of the disease.

Case Reports

Case 1. A girl of 2 years and 10 months was first seen in February, 1959. She was pale, had scattered purpura and bruises, generalized lymphadenopathy and an enlarged liver and spleen. No other abnormal signs were found. The haemoglobin was 38% (5·62 g.), red blood cells 3,000,000/c.mm., platelets 128,000/c.mm., white blood cells 32,500/c.mm. of which 97% were lymphocytes and included some primitive cells. The bone marrow was typical of acute leukaemia. After a blood transfusion she was treated over the next four months with 6-mercaptopurine supplemented by three short courses of prednisone. Thereafter her blood remained well controlled by the purine antagonist alone. From the start of her treatment she remained well in herself and only had 32 days in hospital during the first 10 months of her illness. She inexplicably developed a Cushing-like appearance although she had not had any prednisone for the previous four months. On December 16, 1959, she complained of ear-ache and was found to be blind in the right eye. The left ear drum was opaque and slightly reddened and there was bilateral papilloedema of approximately 1 dioptre, but no haemorrhages (Mr. Charles Bamford) (Fig. 1). Three swellings on the scalp were presumed to be leukaemic deposits. A skull radiograph showed separation of the sutures (Fig. 2) and the C.S.F., which was under normal pressure, contained 1,000 cells/c.mm., 99% of which were primitive; protein, 110 mg. %; sugar, 49 mg. %; chlorides, 662 mg. %. The haemoglobin was 90% (13·3 g.), red blood cells 3,610,000/c.mm., white blood cells 1,700/c.mm. (neutrophil series 60%, lymphocyte series 40%; no immature cells seen). Platelets 106,000/c.mm. Two bone marrow specimens were poorly cellular, but contained 4% myeloblasts.

As there were presumed intracranial and skull deposits, and because the blood and marrow picture suggested a relapse of the leukaemia, therapy was changed on December 17, 1959, to oral amethopterin 2·5 mg. every other day. The blood picture had deteriorated by December 24 and so prednisone 10 mg. daily was added, but meanwhile, on December 18, amethopterin 10 mg. dissolved in 2 ml. of water and diluted with 8 ml. of C.S.F. was injected intrathecally. This was repeated on December 21 and 24, 1959, and on January 5, 1960. At each lumbar puncture the cell count had improved so that by January 12 there were only nine normal looking polymorphs and 25 mg. % of protein. The serum uric acid on December 22 and 31 was 4·5 and 2·6 mg. respectively. Full vision had returned after the third intrathecal dose, and by January 6 Mr. Charles Bamford reported that the optic discs were entirely normal (Fig. 3). The skull deposits were no longer palpable, and the ear drum was now normal. A skull radiograph showed less separation of the sutures.

* Based on a paper read to the Sheffield Paediatric Society, October, 1960.

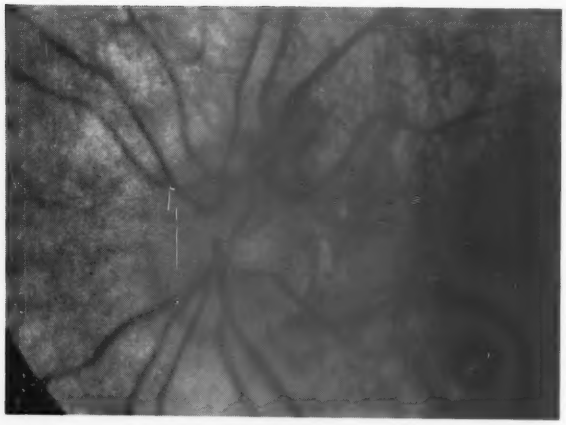

FIG. 1.

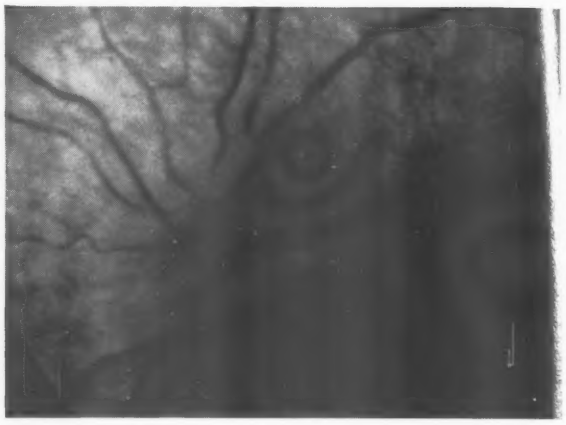

FIG. 2.

FIG. 3.

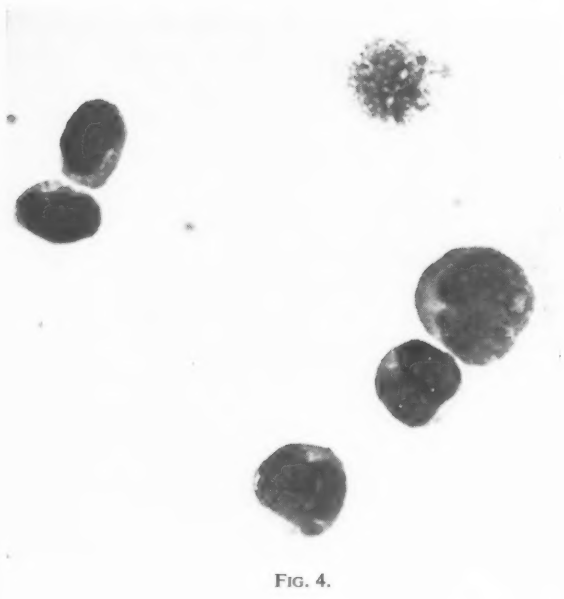

FIG. 4.

FIG. 1.—Case 1, the papilloedema before treatment (left disc).
FIG. 2.—Case 1, separation of the sutures.
FIG. 3.—Case 1, the fundus 15 days later (left disc).
FIG. 4.—Case 1, lymphocytes in cerebrospinal fluid. (× 750.)

The child remained well but bilateral papilloedema was found at a routine examination in August, 1960. There was also another small swelling over the skull. The peripheral blood picture, the bone marrow and the skull radiograph were all normal, but the C.S.F. contained many primitive cells (Table and Fig. 4). The specimens for the above investigations were obtained under one anaesthetic, which was preceded by 50 mg. hydrocortisone intramuscularly as the child had had steroids previously. Intrathecal amethopterin 5 mg., diluted as before, was given at the time of this lumbar puncture and 10 mg. was given four days later and again four days after this. The Table shows how quickly the C.S.F. cleared. The skull deposit was no longer palpable. Meanwhile the child had continued her oral amethopterin 2·5 mg. on alternate days, but daily blood counts showed that all elements were depressed. Eight days after the initial intrathecal dose, the haemoglobin was 70% (10·3 g.), red cells 2,720,000/c.mm., white cells 2,000/c.mm. of which 49% were neutrophils, 45% lymphocytes and 9% monocytes; platelets were 26,000/c.mm. She was too ill for bone marrow aspiration. The serum uric acid four days after the first dose of intrathecal amethopterin was 6·2 mg./100 ml. Despite stopping the oral amethopterin and giving blood transfusions, citrovorum factor 5 mg. three times a day and large doses of prednisone, the blood picture

TABLE
C.S.F. CHANGES AFTER INTRATHECAL AMETHOPTERIN

Date	Intrathecal Amethopterin (mg.)	Cells					Sugar	Protein	Chloride
		Total	R.B.C.	Blastocytes (%)	Polymorphs (%)	Lymphocytes (%)	mg. (%)	mg. (%)	mEq./l.
August 11, 1960 ..	5	2,115,000	—	70	—	30	20	180	111
August 15, 1960 ..	10	445	395	5	35	10	46	150	116
August 19, 1960 ..	10	33	17	—	16	—	42	100	112

reflected a presumed total marrow aplasia and the child died 15 days after papilloedema had developed for the second time, eight months after it had been found on the first occasion and 18 months after the onset of her disease. Permission for autopsy was refused.

Case 2. A girl of 7½ years was first seen in October, 1958. Her paternal grandfather had died of leukaemia. Six months after she first attended hospital her mother died of malignant melanoma. The girl looked ill and pale and had moderately large glands in the left supraclavicular fossa, left axilla and in both groins. There was pain on abduction and flexion of the left hip, but there was full movement in this and all other joints. The spleen was considerably enlarged. The haemoglobin was 56% (8·2 g.), white blood cells 15,700/c.mm., of which 88% were primitive cells; platelets 114,000/c.mm. The bone marrow appearances were typical of leukaemia. No deposits were visible radiologically in the hip or thigh.

Following a blood transfusion, she was treated with 6-mercaptopurine and prednisone for 27 days. Thereafter treatment was continued with the antipurine drug alone. She remained well and attended school regularly until January, 1960, 15 months after her first attendance at hospital, when she noticed a firm, painless 'lump' on her head. Two weeks later, this was larger and there were two more present. No other abnormal signs were found. A skull radiograph was normal. Haemoglobin 112% (16·6 g.), W.B.C. 3,200/c.mm. (neutrophils 70%, lymphocytes 30%); platelets 141,000/c.mm. The C.S.F. was under normal pressure, and contained 26 'primitive' cells per c.mm. only; protein 15 mg. %. Unfortunately the sugar content was not measured. Intrathecal amethopterin 10 mg. was given in the same dilution as for the first patient. Second and third doses were given four and three days later respectively. At the time of the third dose, the C.S.F. contained 11 normal looking lymphocytes per c.mm., protein 15%, chlorides 20 mg. % and sugar 57 mg. %. The serum uric acid was 2·5 mg. % six days after this third dose. The two smaller skull deposits had gone, and the large one was smaller. The child remained in good health. However, 3 days later, two fresh skull deposits had appeared, and in addition the remaining one had enlarged again to about its original size. The left tonsillar gland was also large and firm. The blood count remained satisfactory. The C.S.F. contained only one normal lymphocyte, and the chemistry was normal. Therapy was changed to oral amethopterin and on this the child remained moderately well at home. By May, 1960, however, there was an obvious deterioration, although the skull deposits remained unaltered. Reintroduction of steroids in high dosage gave temporary benefit, but she died at the end of July, 22 months after her illness was first diagnosed.

At autopsy there were generalized petechial haemorrhages over the whole body. Leukaemic deposits were scattered throughout the brain, lungs, spleen and liver.

Discussion

As orally administered antimetabolite drugs such as 6-mercaptopurine and amethopterin control the peripheral blood and bone marrow, but not the intracranial manifestations of leukaemia, it is likely that these neurological complications will become commoner as survival from acute leukaemia becomes longer. It is therefore imperative to search for treatment for these complications.

It seems reasonable to assume that the neurological complications in the first child were the result of leukaemic infiltration of the brain, meninges or cranial nerves, and that the palpable masses in the skulls of both children were leukaemic deposits. It might be argued that the reintroduction of steroids in the first patient was the cause of her remarkable improvement, or that it was the result of a combination of the drug with the intrathecal amethopterin. However, it is well known that the neurological manifestations of leukaemia occur despite all oral treatment, so that it is probable that the intrathecal treatment was responsible for the resolution of these symptoms. That these remissions are temporary was noted by Whiteside *et al.* (1958) who found the effect to last for only four to six weeks in the four children they treated for presumed intracranial leukaemic infiltration. Nevertheless, one of the four patients reported by Cramblett (1959), and eight of the 23 patients reported by Murphy (1959) had a remission of intracranial complications of

up to eight months. The last author considered that the best results were obtained in the patient with headache, increased intracranial pressure, papilloedema, vomiting, separation of the cranial sutures and a pleiocytosis of the cerebrospinal fluid; all the signs shown by the first child reported here who also survived for eight months after treatment of the first intracranial complications. The deposits on the skull of the first child disappeared completely and they diminished temporarily in the second. As this could only have been the result of the intrathecal amethopterin in the latter child, this was probably true also of the first. However, the remission was so brief in the second child that in view of the apparent improvement after intrathecal amethopterin this drug was given orally too. Presumably the drugs given intrathecally can reach skull deposits via the diploic veins which communicate with the meningeal veins.

The type of cells in the cerebrospinal fluid of both patients proved difficult to identify at first, but when seen on the second occasion in the first child they were easily recognized as lymphoblasts. The protein content of the fluid was high at first but fell as improvement occurred. On both occasions in the first patient the sugar content was low initially, which confirms the findings of other workers.

The number of intrathecal injections that should be given remains conjectural, but the average of the authors quoted seems to be three or four. Murphy (1959) gave 10 injections to one patient without harm. The dose quoted averaged 0·5 mg./kg. at three- or four-day intervals. In both the patients reported here this dose, given on three occasions, was sufficient to restore the C.S.F. to normal apart from the second relapse in the first child when the fluid was still not quite clear. Even on this occasion, there was a most remarkable improvement in the cell count after the first dose, i.e. a fall in four days from over 2,000,000 white cells, 70% of which were lymphoblasts, to 50 cells of which only 5% were lymphoblasts. Of greater interest though was the apparent depression of all elements of this child's bone marrow after 15 mg. of amethopterin had been given intrathecally. Unfortunately the child was too ill and the platelet count too low to warrant a further bone marrow biopsy and this examination was not allowed after death. It is known that a small amount of amethopterin given orally crosses the blood brain barrier, but it must remain hypothetical whether the intrathecal amethopterin crossed back to the blood from the cerebrospina fluid through a normal barrier or one that wa affected by the disease. Alternatively, the marrov relapsed a week after it had been shown to be normal.

It does seem, though, that frequent marrov biopsies are important during intrathecal treatment It is difficult to assess whether oral amethopterin should be given if 6-mercaptopurine is still controlling the blood picture as it was in the second patient. Certainly frequent examination of the fundi of children under treatment for this disease is obviously essential.

When a large amount of leukaemic tissue is destroyed by antimetabolites in a short time, hyperuricaemia has been reported. In these two patients the serum uric acid levels were normal.

Summary

Two children with acute leukaemia were treated with 6-mercaptopurine for 10 and 15 months respectively before they developed swellings on the skull which were presumed to be leukaemic deposits. The first child also had neurological signs and both had changes in the C.S.F. suggestive of intracranial deposits.

After treatment with intrathecal amethopterin, the neurological signs disappeared and the C.S.F. cleared. In one child these signs reappeared eight months later, but although the C.S.F. responded to intrathecal treatment, the child died. The swellings also disappeared in the first patient and diminished temporarily in the second. The reason for this disappearance is discussed. Stress is laid on the importance of frequent examination of the fundi of patients with this disease.

I wish to thank Dr. C. W. P. Bradfield for the radiograph reports and Mr. W. Spink, F.B.O.A.(Hons.), Senior Ophthalmic Optician to the Derbyshire Royal Infirmary, for the fundus photographs (originally in colour) of Case 1. Dr. G. R. Osborn and Dr. B. Leonard kindly reported on the C.S.F. and haematology findings and gave much valuable advice. It is a pleasure to acknowledge the prompt gift of the intrathecal amethopterin (methotrexate) from Dr. Ruth Porter, M.R.C.P., of Lederle Laboratories, London.

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BOOK REVIEWS

Prematurity. By BERYL CORNER. (Pp. xii+587; 139 figures + 55 tables. 105s.) London: Cassell. 1960.

The care of the premature has come of age; and who is more fitted than Dr. Corner who has mothered so many of these infants into maturity to give us the first British textbook on the subject. For, with five parts, 38 chapters, 555 pages and four appendices and launched with a foreword by Professor A. V. Neale, her close colleague at Bristol, Dr. Corner's book has, indeed, all the trappings of a full-scale textbook. The five main parts deal successively with the definition, incidence, cause and prevention; diagnosis; care; disorders; and prognosis. Part I covers the incidence, causation and prevention of prematurity and contains an interesting discussion on the difficulties in finding suitable measurements either in terms of duration of pregnancy or of the infant itself, with which to define prematurity difficulties which are particularly obvious in undeveloped countries where birth weights are low. Part II on diagnosis, consists of 10 chapters on the physiology of the foetus, and baby, and of the change over to extra-uterine existence in relation particularly to the immature infant. Though Dr. Corner in her preface is almost hesitant over them, these chapters are, in fact, a real feature of the book and in them will be found, in highly condensed form, a summary of much of the present knowledge of the subject matter. Parts III, on care, and IV on disorders form the great bulk of the book. In them are described the general principles and the management of the well and ill premature infant, as well as the organization of premature care on a civic and a national scale. Dr. Corner was offered a unique opportunity at an early stage to build up the premature services for Bristol, and these sections are expressions of her own large experience and, indeed, of her personal contribution to paediatrics in this country. There are, in addition, two chapters, one on eye conditions by Dr. C. A. Brown, and the other on pathology of the premature by N. J. Brown which within the framework of Dr. Corner's pattern are valuable contributions to the book.

Part V is a short section on the prognosis of prematurity, and the four appendices give details of medical procedures, nursing procedures, antibiotics in the premature infant and the composition of milks.

Dr. Corner's style is gubernatrixial; that is, she is didactic and sure and economical in her writing, and her text is carefully paragraphed and also headed and subheaded in heavy type. It reads more like a synopsis than a textbook and everything is done to make assimilation easy. Yet it is, she admits in her preface, 'written primarily for specialist paediatricians and obstetricians' and indeed it is precisely what any paediatrician who runs a premature unit himself, or particularly who is setting out to build up paediatric services in a community, might like to have at his elbow as a book of reference and as ammunition to help him through committees. Dr. Corner has perfected a style which is extremely clear and easy to understand and she has, throughout her text, supported her own opinions and ideas by a great wealth of references. The result is a massive volume which is certain of immediate acceptance and of many fresh editions in the years to come.

Criticisms of so generous a book are perhaps churlish. There are certain sections which have no real relevance to prematurity, and English readers must continue to envy American textbooks particularly for the quality of paper and binding and for the profusion of appropriate photographs and illustrations. Here the paper and binding are cheap and illustrations, though of good quality, are desultory, as if picked up haphazardly to cheer the book up rather than as serious contributions to clarity and understanding. There is, for instance, the usual photograph of a mongol and of a mongol's feet, of cleft palates and of manual expression of milk, and yet none of a host of interesting conditions which are not commonly seen and for which a photograph would clarify as nothing in the text could do. But these shortcomings are presumably related to costs of production and by standards of today this book at 105s. is good value.

Babies and Young Children. 2nd ed. By RONALD S. ILLINGWORTH and CYNTHIA M. ILLINGWORTH. (Pp. 331; 24 plates. 18s.) London: J. & A. Churchill. 1960.

If we follow Oscar Wilde's advice and collect second editions we shall certainly include this one. It is addressed to parents but should be read and re-read by children's nurses and health visitors and should not escape the notice of paediatricians and family doctors. Indeed the importance of this book lies in the fact that the everyday experiences and alarms of parents in bringing up children are not left to the cosy advice of the magazine column but taken seriously by a professor of paediatrics who for many years had made a special study of child development. Since, however, most husbands leave such matters to their wives it was wise of him to include his own, and reading between the lines, their three children in the venture. The new chapter on 'Holidays' is excellent. The chapter on 'The young child at school' deals with too big a subject in too short a space and in a society where education is so important and causes so much parental concern a companion book for families with schoolchildren would be welcome. Perhaps before long Professor and Mrs. Illingworth will feel they have the knowledge and the experience to write it.

The photographs are a delight though some make the same point twice; the illustrations are a matter of taste,

I find their style too 'American', too near the cartoon for my liking, but it would be interesting to hear the views of a group of mothers who use the book.

The only real regret is that such a useful book has not yet come out as a 'paperback' at a cost within the reach of every family.

Disease in Infancy and Childhood. 3rd ed. By RICHARD W. B. ELLIS. (Pp. vii+714; 301 figures. 55s.) Edinburgh: E. & S. Livingstone. 1960.

This latest edition of Professor Ellis's textbook appears only four years after the previous one, and is completely up to date. The work has not the size of the massive compilations more usual nowadays, but it has the advantage of being written by one man and so has a uniformity of outlook which makes for easy study. The book is written with immense erudition; the reader will find almost every paediatric symptom and syndrome mentioned, and there is an extensive index which makes reference simple. The print is big and clear, the illustrations are profuse, several in colour; and many of them are very striking. As befits its author, whose Chair is of Child Life and Health, the chapters on Social and Environmental Factors in Disease, Constitutional Factors in Disease, and Disorders of Growth and Development, are quite outstanding. Great stress is rightly laid on prenatal and neonatal paediatrics which takes up over one-third of the book.

Such defects as the book has, are the shadows of its virtues. Its format is large, and because of the good art paper used, it is heavy and uncomfortable to hold. So much has been crammed into a volume of medium size that many references are necessarily sketchy in the extreme—so much so that one wonders whether pruning might not have been advantageous. Professor Ellis is acutely aware of the immense variety, both in health and disease, shown by his young subjects, so that 'is likely to' and 'in most cases' have spoiled the sparkle of his style. His use of 'outwith' sent me to a (Scottish) dictionary: I do not know whether 'calorie' for 'Calorie' is a similar Edinburgh usage.

The book is extremely good value, and the student who masters it will have a complete framework in which to file his future experiences.

The Child with Abdominal Pains. By JOHN APLEY. (Pp. 82; 15 tables. 12s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

In this neat little monograph Dr. Apley deals with the problem of what he would like to have called 'little belly-achers' by applying, as best he can, the scientific method to the study of a loosely defined and certainly many-headed monster of a syndrome by objectively comparing his own material with control groups of children; he has managed to keep us informed and entertained. But he has achieved much more; for as, one by one, he matched each aspect of the syndrome against his controls, and tested various hypotheses of causation in the cold light of validity, he gradually abandoned his own bias towards 'organic causes (and organic cures) . . .' and has come to believe that, except for a very small proportion with frank organic disease, children with the periodic syndrome have emotional tension as a constant background, and that, for the most part, the pains are abolished or greatly relieved with the kind of informal psychology that can be applied in a paediatric clinic.

Amongst many other things Dr. Apley tells us that against control groups those with the abdominal pain syndrome have other troubles like headaches, vomiting and travel sickness; that the E.E.G.s are normal in 74% of both groups and epileptiform slightly more often in those without than those with the syndrome; that drugs like phenobarbitone, sodium citrate, phenytoin, troxidone, oblivon as well as 'old-fashioned mixtures' might seem effective, but that their effects are variable, unpredictable and often transient; that less than 8% of his cases have any organic findings responsible for the condition and that one in 10 is considered to need referring to a psychiatric colleague for advice and treatment and that these are usually easy to recognize and always come from families showing evidence of marked anxiety states. All these and many other similar statements are backed up with appropriate figures.

Dr. Apley's style is dextrous and persuasive; those who find his conclusions difficult to subscribe to, or have picked up lazy ways with phenobarbitone and slick reassurance should first read this delightful and easy little book of 82 pages and then return, chastened, to out-patient clinics to find a new interest in an old and troublesome condition.

The Paediatric Prescriber. By PINCUS CATZEL, assisted by S. COHEN. (Pp. xvi+244; 15s.) Oxford: Blackwell Scientific Publications. 1959.

This pocket book covers the whole range of medicinal treatment during childhood excellently. It makes disconnected reading so it has been tried by use for three months in a children's department and has been found practical and reliable; one minor misprint and a few omissions of preparations used idiosyncratically by the reviewer, but no major faults, have turned up.

The introduction deals sensibly with dosage in children and is in itself worth publishing. The major part of the book deals with a formulary of preparations acting on allergy, on blood, on the cardiovascular system, etc. The list of medicaments includes proprietary preparations, and is interspersed with pithy warnings and guides to therapy, resembling but by no means copying, the Alternative Edition of the British National Formulary. This book is a marvel of industry as a compilation, but it bears an individual and critical stamp on almost every page, i.e. it is the composition of an author, not of an editor.

The mixture and the tablet are not the only considerations. There are sections on correction of fluid and electrolyte disturbances, poisons and antidotes, milk and milk products, as well as drugs used for the newborn and a Table of preoperative medication. Perhaps Gaubius' method and Young's rule for calculating doses might in future be omitted from the appendix, they might deceive the unwary into treating meningitis in

infancy with dangerously small dosage, although they have a place in medical history.

We wish Dr. Catzel's book a long life, but that raises the question 'Can he keep it up?' Therapy changes quickly, yesterday's advance may be tomorrow's placebo, and much revision will be needed before each new edition is reborn. Just now, this is a book to buy and to keep at hand.

Modern Problems in Pediatrics. Vol. VI. Edited by A. HOTTINGER and H. BERGER. (Pp. xvi+560; 176 figures + 52 tables. Sw. fr. 98.) Basel and New York: S. Karger. 1960.

This sixth volume in the 'Modern Problems in Paediatrics' series is devoted to physiological and pathological aspects of renal function. There are 26 papers, nine on physiological and the remainder on pathological subjects. Anyone interested in renal disorders in infancy will find much valuable and up-to-date information. Although there is no index the table of contents is detailed and there is an excellent bibliography throughout.

The first chapter deals with the renal bloodflow in health and disease and Reubi discards both Trueta's 'shunt' and Pappenheimer's 'plasma-skinning' theories and concludes that perfusion pressure, viscosity and arteriolar resistance are the chief regulating factors. Colin and Polonovski discuss the regulation of water metabolism in the newborn and in infancy and point out the difficulties in deciding which of the possible mechanisms is responsible for their comparatively poor powers of urinary concentration, diuresis and tubular reabsorption of water. They do not reach any definite conclusion. Elkinton discusses the metabolic production of hydrogen ions and McCance and Widdowson consider some of the aspects of renal function before and after birth, concluding with a timely warning against studying the kidney in isolation and comparing a newborn infant's kidney with an adult's in regard to responses to 'violent and arbitrary' tests. Renal angiography and venography, their techniques, value and dangers are well described by Murray and Steiner respectively. The function of the tubular epithelium is lucidly expounded by Stalder and the part played by the kidney in mineral metabolism, described by Hungerland, will delight the mathematically minded, but may prove difficult for those whose familiarity with logarithmic tables has declined with the passing of the years. The value of the Volhard concentration test in assessing the functional state of the distal and collecting tubules is discussed by Sarre. In the second part of the book, dealing with pathological aspects, McCrory contributes an excellent account of the pathogenesis of glomerulonephritis, its diagnostic problems, treatment and prognosis. Kretchmer, Barnett and Shibuya consider that the nephrotic syndrome involves a strong constitutional element and that, although steroids have proved of therapeutic value, many problems still remain unsolved.

Nephrocalcinosis is discussed by Roger and diabetes insipidus by Lestradet. Fanconi and Illig deal with familial lipoid nephrosis and nephrophthisis and Prader with hereditary hypophosphataemic vitamin D-resistant rickets.

Linneweh stresses the importance of recurrent pyelonephritis in causing renal failure in adult life and the prophylactic implications involved. Zollinger undertakes the thankless task of resurrecting interstitial nephritis as a pathological entity.

Surgery is represented by an excellent chapter on obstructive uropathy by D. I. Williams and the physiopathology of the causative lesions is described by Jean. The treatment of acute renal insufficiency is well set out by Gautier.

Advances in Pediatrics. Vol. XI. Edited by S. Z. LEVINE. (Pp. 285; 36 figures + 23 tables + 18 plates. 68s.) Chicago: The Year Book Publishers. 1960.

This book is firmly established as an annual inmate of many libraries and Volume XI will be readily welcomed.

There are six excellent articles covering a wide range of subjects. This is not the first book to show an increasing co-ordination between physiologist, biochemist and clinician; this is well demonstrated in *Respiration and Respiratory Problems of the Newborn Infant* by C. D. Cook, H. Barrie and M. E. Avery; *Clinical and Experimental Interrelations of Sodium and the Central Nervous System* by Robert E. Cooke and Edward J. Ottenheimer; and *Aminoaciduria and Certain Related Disorders of Amino Acid Metabolism* by Selma E. Snyderman and L. Emmett Holt. So many articles on allergy seem to be highly allergic but *Allergy in Childhood* by William C. Deamer is easily comprehensible and full of good sense. A reminder that some countries still have the problem of infantile gastro-enteritis arrives in an interesting article: *Infantile Diarrhoea and Dehydration: Ambulatory Treatment in a Hydration Center* by Julio Meneghello and others. The final chapter gives further views on therapy in acute rheumatism, and *Present Status of Hormone Therapy in Rheumatic Fever, with Special Reference to Short-term Treatment in Active Carditis* by May G. Wilson is very stimulating.

All these articles are well written and the references are extensive.

Undoubtedly a large field of readers will be attracted to this volume, and S. Z. Levine and his associate editors are to be congratulated.

Cerebral Palsy and Related Disorders. By ERIC DENHOFF and ISABEL ROBINAULT. (Pp. 421; illustrated. 93s.) London: McGraw-Hill. 1960.

Among many recent books on cerebral palsy, this work is quite outstanding. In the early chapters, the theme is the essential unity of the syndromes of cerebral dysfunction, comprising cerebral palsy, epilepsy, mental deficiency and related disorders. There is special emphasis on associated sensory and perceptual disturbances and on the hyperkinetic child. The authors stress the dynamic approach to cerebral palsy, the necessity for teamwork, and the importance of integrating therapy with the developmental stage reached by the child. Lip service has often enough been paid to these ideals in the past, but here is a practical handbook with

precise and detailed instructions on how to achieve them. The methods advocated are those developed at the Meeting Street School in Providence, Rhode Island, and the authors have managed to capture something of the atmosphere of restrained optimism which is so evident to the visitor to the School. There is frequent reference to the practice and opinions of other authorities, however, and in general the therapeutic approach is applicable to British conditions, though the statement that 'The pioneer days of treating cerebral palsy are over. Facilities abound . . .' will raise wistful eyebrows in this country.

In some chapters there is perhaps too much discussion of general paediatric problems, which is too brief to help paediatricians and unnecessarily detailed for therapists. There are few difficulties for British readers, although the definition of the perinatal period as extending from conception through the first month after birth will not be generally acceptable and may be misleading. There is a useful appraisal of the value of pneumoencephalography in cerebral palsy, and an illuminating chapter on the problems and social needs of young adults.

This book is likely to be of most value to those actively engaged in the care of children with cerebral palsy, both physicians and therapists, who could profitably consult it many times daily, for it contains a wealth of practical advice.

Child Research in Psychopharmacology. Edited by SEYMOUR FISHER. (Pp. 216; 7 figures. 52s.) Oxford: Blackwell Scientific Publications. 1959.

It is important to recognize that this account of a conference held at Washington, D.C., and sponsored by the National Institute of Mental Health is written in America.

One appreciates the wealth and generosity of a country prepared to publish in full, not written papers, much less carefully drawn conclusions, but the thinking aloud which a gathering of this kind fosters, indeed, invites. One may regret that the drugs about which it is written, are, of course, given their American trade names; some of them sound unfamilar to readers in this country. This latter is no serious drawback since a comprehensive glossary of drugs currently used in psychiatry is given at the beginning of the book. At the end is a reference list containing 159 items, reviewing current usage of psycho-pharmacological agents with children.

One gathers that the conference was called because of the flood of new tranquillizers, thus encouraging their misuse. The chairman, Dr. Milton Senn, deplores this in a succinct contribution which ends the conference. Pointing out that paediatricians and family doctors are called on increasingly nowadays to treat behaviour disorders and symptoms arising from psychological difficulties, he pleads that the drug companies should not encourage 'the nonpsychiatric physician to use drugs when other areas of psychotherapy are needed, useful and indicated'. Indeed, there is more wisdom packed into the two pages of closing remarks than in other contributions that are more diffuse in texture, and cover more ground.

However, this is not a treatise on drugs. It sets out to consider the problems posed by biological research in this field as applied to children, with the developmental tide running fast. If behaviour patterns are compared, then what constitutes 'improvement'?

May not odd behaviour serve a valuable functional purpose in calling attention to stress? Is it advisable to obliterate signs of tension without fuller investigation? And above all, what constitutes 'normal controls'?

There is a plea for better planning in researches aimed at evaluating the advantages of one drug over another, and because the conference is reported verbatim there is a good deal of repetition. In this country we tend perhaps to skim the contents and read only the summaries. This one cannot be read in that way for it describes a group of experts from various disciplines, psychiatry, paediatrics, psychology, biochemistry, social medicine, and others, comparing essentially their common areas of interest, doubt and uncertainty, in a field made more difficult by reason of commerical initiative and rapid advances. In reading it, one is allowed to share their difficulties.

Herz- und Kreislaufstörungen im Säuglings- und Kindesalter. By P. GEGESI KISS and GY. SZUTRÉLY. (Pp. 879. S17.50.) Germany: Verlag der Ungarischen Akademie der Wissenschaften. 1960.

This book, written by the Professor of Paediatrics at the Budapest University Hospital, and his cardiological colleague is indeed a welcome addition to the literature on paediatric cardiology. It has been translated from the Hungarian into very readable German, and on reading through the various chapters it becomes increasingly obvious that the authors have had very wide experience in their field.

It has been compiled along more or less conventional lines in that a section on cardiac embryology, anatomy and physiology is followed by a chapter on the examination and investigation of the child with heart disease. This latter in particular is well thought out and contains helpful hints.

In contrast to recent publications in the English language, more space has been given to the sections dealing with acquired forms of heart disease, and such conditions as rheumatic fever, diphtheritic myocarditis and the virus carditides are excellently dealt with, though one can possibly argue with the authors on some points where the cause of rheumatic fever and its prevention with prophylactic antibiotics is concerned. Heart involvement in acute bacterial and viral diseases and its management is fully discussed.

In a book of this kind, however, it is a little surprising that the authors have not dealt with congenital heart disease in greater detail, particularly as their patient material extends to 16,000. It has been estimated that approximately six per 1,000 live births suffer from congenital heart disease in some form or another and paediatricians are becoming increasingly interested in the early diagnosis of these abnormalities. Endocardial fibroelastosis, is not mentioned at all. Admittedly the incidence of various diseases varies from country to country.

The section on arrythmias and conduction defects is admirably described and well illustrated with E.C.G. tracings. Therapy in cardiac disease is discussed at length and prominence is given to the value of hibernation using the lytic cocktail not only in preoperative management, but also in the treatment of conditions producing acute peripheral circulatory failure, cyanotic attacks in Fallot's tetralogy, and supraventricular paroxysmal tachycardia.

The book is well produced, and can confidently be recommended to anyone interested in this subject.

Die Hals-Nasen-Ohren-Krankheiten im Kindesalter. By F. BIESALSKI, with a chapter on Speech Disturbances by R. LUCHSINGER. (Pp. xii + 342; 118 figs. DM. 49.) Stuttgart: Georg Thieme Verlag. 1960.

This excellent little book written by an ear, nose and throat surgeon with wide experience in paediatrics, covers the whole of paediatric ear, nose and throat surgery in its widest sense. It is specifically written for the general practitioner and the paediatrician, and details of surgical treatment are omitted.

In the short space of just over 300 pages, the author manages to describe practically all the conditions which are encountered in childhood, and special emphasis is put on those diseases peculiar to the young age groups.

It is perhaps inevitable that some of the conditions described, especially those which are not usually directly handled by ear, nose and throat surgeons, as for instance, congenital abnormalities of the palate, oesophagus, pinna and the neck, are not described very fully, but the general standard of the text is very high.

It is difficult to single out any of the chapters for special praise, but the extensive chapters on diseases of the middle ear and the chapter on 'Speech Disturbances' by Professor Luchsinger, are especially outstanding.

Although the treatment which Dr. Biesalski outlines in this book is very much up to date, he has still included many well established and proven methods of therapy in preference to some, as yet, experimental methods of treatment.

The book is beautifully printed and the photographs and drawings are of the very high standard with which one is accustomed from these publishers.

The references are adequate, but it is noticeable how few English and American references are given, possibly because the book is written for German paediatricians who will not have the time nor the facilities to look up much foreign literature.

Die physiologische Entwicklung des Kindes. Vorlesungen über funktionelle Paedologie. Edited by FRIEDRICH LINNEWEH. (Pp. vii+471; 236 figures. DM. 98.) Berlin: Springer Verlag. 1959.

In recent years, biochemical and physiological methods have become available which are applicable to investigations on infants and small children. This has stimulated interest in the normal development of bodily functions from birth to adulthood; yet new information has tended to be scattered widely through a variety of medical journals. To remedy this situation a symposium was organized in Germany some two years ago at which invited speakers from many countries presented their work in this field. This book reprints the communications ('lectures') given at that time; no discussion is printed.

A large number of topics is covered, beginning with four general chapters, including one on the stress-reaction and one on oxygen lack at the time of birth. The special part contains 48 chapters of unequal length (varying from two to 15 pages). Almost all of the authors have recently done active research on the subject which they review. This ensures an air of topicality often sadly missing from other 'Symposia'. There are seven chapters on nervous system, EEG and temperature regulation, two on respiration, three on circulation, seven on metabolism, nine on kidney and electrolytes, four on gastrointestinal functions, eight on blood and its constituents, including immunological aspects, and eight on endocrines. A concluding chapter deals with the relationship between drug action and growth.

Most of the authors have managed to blend a description of their own research with a review of the results achieved by other workers. The standard of presentation is high, almost without exception. There is not only much detailed information, but the reader will find many useful hints on work recently done or still in progress. This is thus both a stimulating and a rewarding book, which also serves as an almost indispensable book of reference. Although most of the chapters are in German, 14 are in English (six of these on the kidney and allied subjects), two of them by authors from the U.K. (Derek Richter and Thomas Stapleton). Most of the chapters contain many helpful diagrams and tables, which can of course be understood without much knowledge of German. Useful lists of references are appended to each of the chapters and there is a good index.

This seems a 'must' for all medical libraries and should be studied not only by paediatricians but also by clinical pathologists, biochemists and physiologists. The price, although high, is reasonable by German publishing standards.

Syllabus of Laboratory Examinations in Chemical Diagnosis. Revised edition. Edited by LOT B. PAGE and PERRY J. CULVER. (Pp. xxiv+580; 56 figures + 98 tables. $12.50.) Massachusetts: Harvard University Press. 1960.

This book originated in a course of lectures given to second-year medical students at Harvard School of Medicine. Intended to serve as a link between the preclinical and clinical course, it is now addressed to the clinician with an inquiring mind, and time to inquire; and the laboratory worker with a keen clinical interest and opportunity to keep this interest alive at the bedside. Since such people are relatively few, the book's limitations are inseparable from its virtues. In addition to sections on haematology, chemical pathology, and bacteriology, it includes chapters on cardiac catheterization and pulmonary physiology. Each section is introduced by a detailed consideration of the physiological

principles on which the various tests are based and concludes with a critique of their clinical scope and limitations.

As often happens with books that have outgrown their original purpose and where there are many authors instead of one, variations in standard and presentation are the price of comprehensiveness. The chemical section is perhaps the most impressive: it shows up the close liaison which can be achieved between ward and laboratory which is so striking a feature of the best of American medicine. The laboratory worker sometimes forgets that the most sensitive test is only as useful as the clinician can make it by interpreting the results correctly; and conversely, the clinician evaluating results, does not always take into account that their value is limited by the accuracy with which they can be reproduced in the laboratory. A book like this can help to bridge the gaps. It is, however, too detailed for resident staff with emergency duties in the laboratory. They neither need nor want to know six different methods for estimating haemoglobin. Several of the methods, especially in the section on haematology, do not conform to British practice (coverslips for example, are used for blood films and differential counts). In spite of this, clinical pathologists who are truly clinical and physicians who wish to understand the investigations they are ordering or doing themselves will find the book of great value.

Chemical Micromethods in Clinical Medicine. By R. H. WILKINSON. (Pp. 136; 18 figures. 40s.) Oxford: Blackwell Scientific Publications. Springfield, Illinois: Charles C. Thomas. 1960.

The recognition of the necessity for routine micro- and even ultra-micromethods of the chemical analysis of blood comes, perhaps, most easily to the pathologist in a children's hospital where the amount of blood available for analysis is often limited. This little laboratory manual is essentially a description of the microchemical methods in use in the laboratory of The Children's Hospital in Great Ormond Street. The introductory chapters deal with the techniques of the collection of blood specimens and the apparatus required, and contain pertinent remarks on the control of the results. In the following chapters, the methods described are grouped together according to the function they are designed to investigate, e.g. liver function tests, tests of protein metabolism, etc., with each chapter prefaced by brief remarks on their use and interpretation. The final chapter deals briefly with ultra-micromethods. The practical details of each method described are clearly set out and are easy to follow.

Given its somewhat limited scope, this book will be found useful, especially for biochemical technicians and, possibly, pathologists in a general hospital with a children's ward where babies are often subject to frequent venesection because of the lack of experience in micromethods. Its appeal, however, is diminished by the limited scope of the book. Only one method is described for each estimation. Possible difficulties are not mentioned, nor the possible errors involved. Other than the reference to the original description of the method selected, few references are given to the literature. The prefatory discussion in each chapter on the clinical uses of the tests is too brief to be useful. Chemical pathologists would find it of use only as an adjunct to the larger works or to the original literature, and interesting mainly as the description of the routine chemical pathology in a large children's hospital. The appendix gives the normal values in children and adults, using these micromethods.

It must be pointed out that the normal full-term newborn infant has a much higher serum protein level than that stated and it should be made clear also that the serum protein level of premature infants varies with the birth weights. It is very misleading to give an overall value when the birth weight of the premature infant can vary from 2 to 5½ lb. The serum gammaglobulin level of the newborn infant is also incorrectly given. It is actually slightly higher than that of the adult, and not half, as stated.

The book is well printed on good paper, but 40 shillings seems excessively expensive.

Oxygen Supply to the Human Foetus. Edited by JAMES WALKER and ALEC C. TURNBULL. (Pp. 313; illustrated. 47s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

This book records the proceedings of a meeting held at Princeton, New Jersey, in December, 1957, under the sponsorship of the Macy Foundation and the C.I.O.M.S. The discussions covered a wide range of subjects, from the general physiology of oxygen transport in the adult and the foetus to the vascular anatomy of the placental circulation (an admirable and concise account from Elizabeth Ramsey), from new methods for measuring oxygen tension in the blood and tissues to a general discussion on the significance of umbilical cord blood studies. There is much factual information here which has been carefully arranged and which is not readily available elsewhere. It is not easy reading because of the wide variety of subjects and techniques which were considered, and because of the interpolated discussions. On the other hand it is difficult to see how the material could have been arranged otherwise without considerable sacrifices. Many of the discussions were both informative and stimulating, on the technical aspects of blood gas analysis for instance, and on the changes which may occur during foetal distress. The recent studies on the changes in pressure and oxygen content of the blood in the intervillous space were of particular interest. And there have been some careful measurements of uterine blood flow in man, though the indirect methods used should be compared with a direct method (in animals).

The difficulties which the editors experienced in arranging this diverse material derives from our lack of basic knowledge in this subject, in which so much is still speculative. The relative inaccessibility of the foetus *in utero* is as frustrating to the obstetrician who wishes to know what is going on inside, as it is to the physiologist who wishes to know how it does so. This book sets out many of the facts so far established, and proposes a number of questions to which answers are needed, and which should not be too hard to supply.

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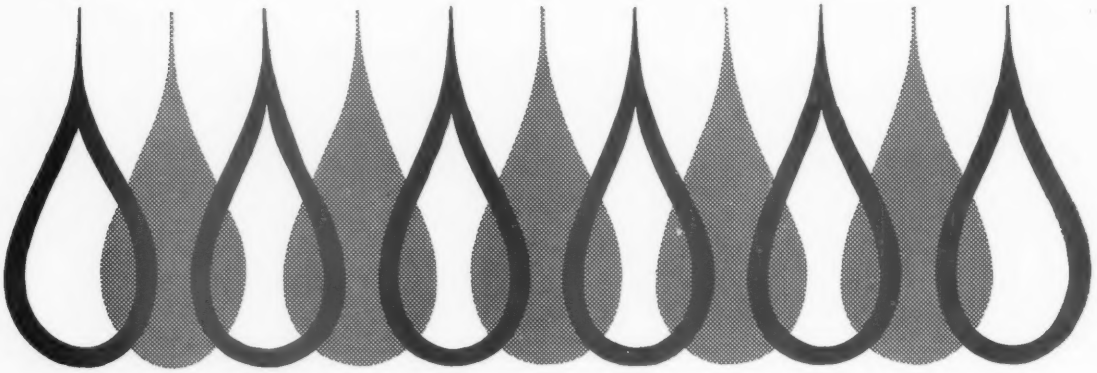

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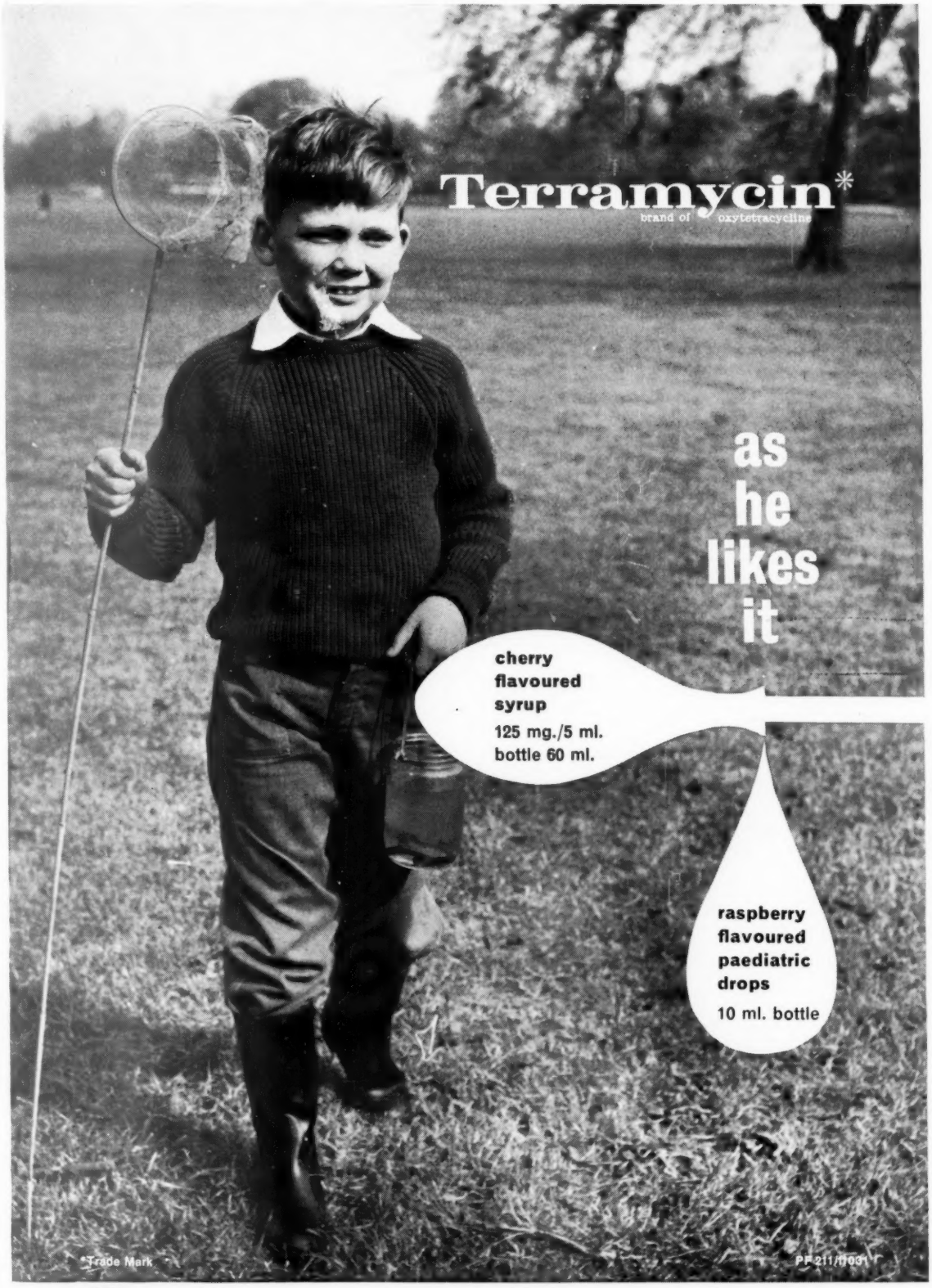

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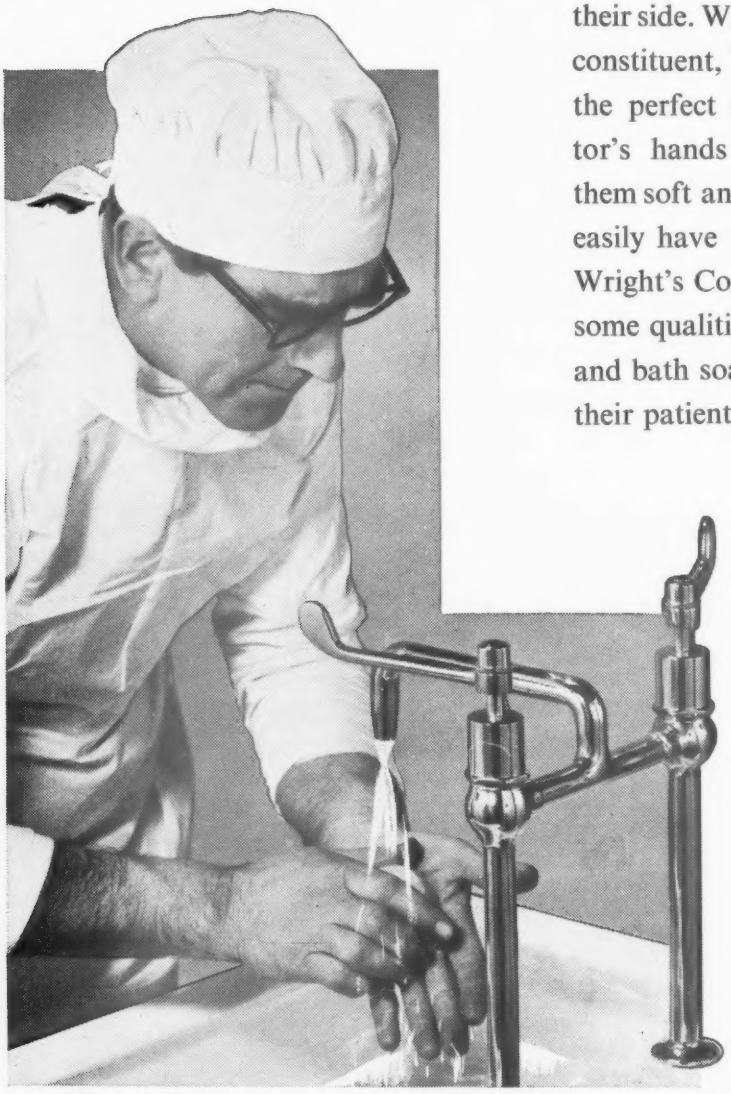

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